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Differences in Risk Factor-Colorectal Adenoma Associations According to Nonsteroidal Anti-inflammatory Drug Use

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Differences in Risk Factor-Colorectal Adenoma Associations According to Nonsteroidal Anti-inflammatory Drug Use

By

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M.B.B.S.
Dow University of Health Sciences
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An abstract of
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Abstract

Differences in Risk Factor-Colorectal Adenoma Associations According to Nonsteroidal Anti-inflammatory Drug Use

By Sobia Mujtaba

Multiple observational studies and large, randomized controlled trials indicate that non-steroidal anti-inflammatory drugs (NSAIDs) strongly reduce risk for colorectal neoplasms. However, the strengths of these findings suggest that NSAIDs may so mask various risk factor-colorectal neoplasm associations, that they may be undetectable among NSAID users. We investigated whether various risk factor-colorectal neoplasm associations differed by non-aspirin NSAID use using pooled data from 3 colonoscopy-based case-control studies of incident, sporadic colorectal adenoma conducted in Minnesota, North Carolina, and South Carolina between 1991 and 2002. Participants (n = 789 cases, 2,035 polyp-free controls) provided risk factor data prior to colonoscopy. The multivariable-adjusted odds ratios (OR) (95% confidence intervals [CI]) for those in the highest relative to the lowest quartiles of exposure, by regular non-aspirin NSAID non-use/use, respectively, were 1.57 (CI 0.96, 2.55) vs. 1.14 (0.37, 3.49) for total fat, 1.37 (CI 0.86, 2.18) vs. 0.70 (CI 0.23, 2.25) for saturated fat, 0.93 (CI 0.68, 1.28) vs. 1.30 (CI 0.61, 2.75) for calcium, 0.89 (CI 0.64, 1.23) vs. 1.38 (CI 0.65, 2.94) for total fruits and vegetables, 1.04 (CI 0.73, 1.49) vs. 0.70 (CI 0.31, 1.56) for total red and processed meats, and 0.85 (CI 0.65, 1.11) vs. 0.94 (CI 0.52,1.71) for physical activity. For current versus never smokers, the ORs (CIs) among regular non-NSAID users/non-users were 2.91 (CI 2.22, 3.82) vs. 1.75 (CI 0.90, 3.41), and for those who were obese versus those who were normal weight, they were 1.67 (CI 1.28, 2.17) vs. 1.19 (CI 0.69, 2.04). The associations of age, height, intakes of alcohol, dietary fiber, and total folate, hormone replacement therapy, and oxidative balance score with adenoma did not substantially differ according to NSAID use.

These findings suggest that regular non-aspirin NSAID use may mask, beyond simple confounding, associations of major risk factors with colorectal adenoma, and support routinely assessing such associations stratified by regular non-aspirin NSAID use.

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Background (Chapter I)

Colorectal cancer (CRC) is the second leading cause of cancer deaths in the United States (1). Globally, it is the third most common incident cancer (after lung and breast cancers) with nearly an estimated 1.4 million new cases, and 694,000 deaths in 2012 (2). In the U.S., the annual incidence of large bowel cancers is estimated to be approximately 132,700, of which 93,090 are colon and the remaining are rectal cancers (3). Annually, approximately 49,700 deaths in the U.S. are attributed to CRC; overall mortality from CRC accounts for nearly 8% of all cancer related deaths (3).

The risk of developing CRC is influenced by environmental (including diet, and lifestyle) and genetic factors (4). In the U.S., the lifetime incidence of CRC in an average risk individual is about 5% (5); the lifetime risk of developing a colorectal adenoma, the precursor lesion to CRC is nearly 19% (6). The incidence of CRC in the U.S. is about 25% higher in men, as compared to women and nearly 20% higher in African Americans than in whites (7). Although the risk of CRC is higher in those who have an underlying genetic predisposition, an inherent genetic susceptibility is found in only a small proportion of individuals. International differences in incidence rates, and migration studies indicate that environmental, particularly dietary factors are the dominant factors that influence risk of CRC in most people. (8, 9)

Family History of Colorectal Adenoma or Colorectal Cancer

A family history of CRC is a risk factor for CRC; familial clustering of CRC is recognized both, as cases who are part of well-defined hereditary genetic syndromes, such as Familial Adenomatous Polyposis (FAP) and Hereditary Non-Polyposis Colon Cancer Syndrome (HNPCC or Lynch Syndrome), and as those who are not part of a defined genetic syndrome. In the U.S., about 5% of adults report having a first or second degree relative with CRC (10).

Epidemiologic data suggest that those who have an affected first-degree relative (parent, sibling or child) have a 1.6 - to 8-fold higher risk of developing CRC (11, 12); the increase in the magnitude of the risk depends upon the number of affected relatives, the type of relative, whether they are first-degree relatives or not, and the age at diagnosis in the affected family members (13-17).

Adenomas or adenomatous polyps are considered to be the precursor lesions of CRC (18). Not all adenomatous polyps undergo malignant transformation; the likelihood of developing CRC from these lesions is associated with the histology and the size of the polyps (19, 20). In a meta-analysis 20 case-control, and 7 cohort studies that investigated the risk of CRC among relative of CRC cases, 9 case-control studies that investigated the risk of CRC among those who has relatives with colorectal adenoma, Johns et al. (14) found a statistically significant, approximately 2-fold higher risk of CRC among those with an adenoma in a first degree relative (relative risk [RR] 1.99; 95% CI: 1.55, 2.55). This result was supported by findings in a subsequent meta-analysis (21) where 2 studies were identified that directly assessed whether there was an association of CRC and having a first degree relative with an adenomatous polyp (or adenoma). In the first study (22), a 4 times higher risk for CRC was found among those with first degree relatives with adenomas (2.31% versus 0.53%; RR 4.36; 95% CI: 1.60, 10.21]). In the second study (23), a 2 -fold higher risk of CRC was found among those persons who had first degree relatives with large adenomas (≥1 cm) as compared to those who had no first degree relatives with adenomas or CRC (8.3% versus 4.2%; odds ratio [OR] 2.27; 95% CI: 1.01- 5.09).

Age

Age is an independent risk factor for developing CRC, regardless of whether an individual has a family history of CRC (hereditary syndromes or otherwise). The incidence of

CRC begins to rise between the ages of 40 and 50 years, and age-specific incidence rates continue to increase thereafter in each succeeding decade (24). More than 90% of CRC cases occur in people aged 50 years or older (25, 26). Recent data from the United States Surveillance, Epidemiology and End Results (SEER) database suggests that the incidence of CRC is increasing in the under 50 age group while concomitantly decreasing in older groups (5, 27). The decline in CRC incidence rates in the above 50 age group is attributed to changes in risk factors, as well as introduction of screening for CRC by colonoscopy (5, 28). The rise in CRC incidence among young adults is paralleled by a rise in the prevalence of CRC related risk factors such as obesity, sedentary lifestyle etc.; however, there is a lack of concrete epidemiologic evidence to suggest a causal association (29-31).

Obesity

The association of obesity with CRC is consistently found in observational epidemiologic studies. A statistically significant, higher risk of incident CRC with increasing BMI (in both sexes) is reported in several systematic reviews and meta-analyses of observational studies (32-35). In 2007, the World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) concluded that based on the existing epidemiologic evidence, BMI is associated with a higher risk of several cancers, including CRC (36).

Obesity a state of chronic low-grade inflammation. There are multiple pathophysiologic mechanisms that link obesity to colorectal carcinogenesis (37): insulin resistance alters the insulin-like growth factor-1 (IGF-1)/ IGF-1 receptor axis (IGF-1R) which contributes to colorectal carcinogenesis; insulin resistance also causes increased oxidative stress. Obesity is associated with impaired redox balance, and increased lipid peroxidation (LPO) that releases free fatty acids, which can lead to oxidative stress through increased production of reactive oxygen and nitrogen species (RONS). Oxidative stress promotes inflammation, DNA damage

and tumorigenesis. (37). Obesity-associated carcinogenesis is also associated with an imbalance of leptin, and adiponectin; leptin induces the production of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNFα), and interleukin-6 (IL-6) that are involved in inflammation, and carcinogenesis. The NF-kB signaling pathway is also thought to play a role in mediating obesity-related cancer risk (38). Obesity is associated with higher levels of rectal prostaglandin E_2, which inhibits apoptosis in colonic epithelial cells (39); this may be due to upregulation of the cyclooxygenase-2 by inflammatory cytokines derived from adipocytes. (40)

Physical Activity

Regular physical activity is consistently associated with a lower risk of colorectal adenoma (41-49), and CRC in observational epidemiologic studies (50-52). In a meta-analysis of 24 case-control, and 28 cohort studies, Wolin et al.(53) found an statistically significant, inverse association of physical activity with risk of CRC (RR 0.76; 95% CI: 0.72, 0.81). In a meta-analysis of 12 cohort, and 9 case-control studies, Boyle et al. (54) found statistically significantly lower risks of proximal (RR 0.73; 95%: CI 0.66-0.81), and distal colon cancer RR 0.74; 95% CI: 0.68-0.80) among the most physically active individuals.

The association of physical activity with risk of CRC may be explained by multiple mechanisms. More frequent physical activity may be associated with lower levels of systemic inflammation, as indicated by lower levels of C-reactive protein (55, 56). Higher levels of physical activity are associated with lower levels of prostaglandin E_2, which inhibits apoptosis in colonic epithelial cells (57); higher levels of physical activity are also associated with higher levels of prostaglandin F_2, which decreases the rate of colonic cell proliferation (51). A sedentary lifestyle is also associated with the “insulin resistance syndrome”, which is characterized by alterations in the IGF-1/ IGF-1 receptor axis, that promotes colorectal

carcinogenesis (37). Physical activity is also postulated to reduce bowel transit time, and thereby reduces the exposure of the bowel wall to possible carcinogens (50). Reductions in fecal pH, body weight, and increased activity of anti-oxidant enzymes are other mechanisms through which physical activity is hypothesized to influence tumorigenesis (58).

Height

Results from observational epidemiologic studies suggest that there may be an association of taller height with a higher risk of colorectal adenoma and CRC. In the Nurses' Health Study (NHS) (59), and the Health Professional Follow-up Study (HPFS) (47), increasing height was associated with statistically significantly higher risks of colon cancer. In a community-based case-control study, increasing height was associated with a statistically significant higher risk of sporadic colorectal adenoma(s) (41). In a large prospective cohort study of 7,052 men, and 8,354 women, Smith et al. (60) found that increasing height was directly associated with mortality from non-smoking related malignancies, especially CRC, and prostate cancers. In a prospective cohort of 31,199 men and women, Jousilahti et al. (61) found that height was directly associated with higher mortality from rectal cancers.

It is postulated that a taller stature in adulthood, that may in part be due to an energy-rich diet in childhood, may be associated with higher concentrations of IGF-1. IGF-1 is linked to oxidative stress, promotion of cell proliferation, and inhibition of apoptosis in genetically damaged cells (62). Height correlates closely with the length of the colon; it is hypothesized that a taller height, and therefore a longer length of the colon increases the total number of stem cells that may be at risk for neoplastic transformation (47).

Energy Intake

There are conflicting results from observational studies regarding the association of total energy intake with risk of colorectal adenoma and CRC.

Higher total energy intake is associated with a statistically significant, higher risk of colonic neoplasia in several case-control studies (41, 63-69). However, inverse associations are found in other case-control studies (45, 70, 71) and in the Iowa Womens' Health Study (IWHS) (72).

In multiple animal studies, increased energy intake, independent of dietary fat content, is consistently associated with a higher risk of chemically induced colon cancer. The anti-tumor mechanisms found with caloric restriction in these studies included a lower number of dividing cells (73), decreased activity of colonic mucosal ornithine decarboxylase, and inhibition of tyrosine kinase activity in the colon (74).

Smoking

The association of cigarette smoking with a higher risk of colonic polyps (75-79) and incident CRC, is consistently reported in observational studies (79, 80) (81) (82). In a meta-analysis of 106 observational studies on incident CRC, Botteri et al. (80) found a statistically significant, higher risk of CRC among ever smokers relative to never smokers (pooled RR 1.18 [95% CI: 1.11, 1.25]). The risk of mortality from CRC was also substantially higher among ever smokers relative to never smokers (RR 1.25 [95% CI: 1.14, 1.37]). Statistically significant associations of smoking with a higher risk of colonic neoplasia are reported in other smaller meta-analyses as well (81) (82). Smoking is also a major risk factor for serrated polyps of the colon, including those that are adenomatous (83, 84).

Smoking is hypothesized to be an initiator of colorectal carcinogenesis (79). Carcinogens from cigarette smoke are postulated to cause irreversible genetic damage in

the normal colorectal mucosa. Smoking is more strongly associated with CRCs with micro-satellite instability (MSI). MSI is a hallmark of HNPCC, and serrated adenomas (85-91)

Alcohol

Alcohol consumption is designated as a risk factor for CRC by the International Agency for Research on Cancer (IARC) (92). In a meta-analysis of 27 cohort, and 34 case-control studies, Fedirko et al. (93) concluded that compared to never drinkers, there was a statistically significantly higher risk for CRC among moderate drinkers (2-3 drinks per day [summary RR 1.21; 95% CI 1.13, 1.28]), and heavy drinkers (≥4 drinks per day [RR 1.52; 95% CI 1.27, 1.81]). The results for heavy and moderate alcohol intake were found to be consistent with previous pooled studies, (94, 95) and meta-analyses (96-98). In contrast to the other studies, Fedirko et al. (93) found a statistically significantly higher risk of CRC even among light drinkers (RR for ingestion of 10 g/day of ethanol 1.07 [95% CI 1.04-1.10]), which was either not reported or not found to be statistically significant in the other studies (94-98).

High intakes of alcohol, together with low dietary folate, and methionine may reduce levels of S-adenosyl-methionine which is required for DNA methylation. Hypomethylation of DNA is associated with loss of normal regulation of proto-oncogene expression observed in colorectal adenomas and CRC (99).

Dietary Fats

The highest incidence of CRC incidence, and mortality in relation to dietary fat intake (including fat constituents such as saturated fat, and cholesterol) is seen in the western world (100, 101), with a strong dose-response relationship between per capita fat intake and CRC incidence and mortality (100, 101). Comparisons suggest that countries with 50% lower dietary fat intake than the U.S. have approximately a third of the risk for CRC (102,

103). Migration studies support the association of a high fat diet with CRC; a higher incidence of CRC is seen migrant populations that moved to regions with a western style diet (104-106). The results from observational studies are not entirely consistent (107). Of at least 26 studies that investigated the association of dietary fat intake with risk of colorectal neoplasia, direct associations were found in 12, inverse associations were found in 2, and no association was found in 15 studies, including the Seventh Day Adventists (108), and the IWHS (72). Results from 2 large prospective cohort studies, the NHS (109), and the HPFS (110) suggest that the consumption of total, animal, and saturated fat is associated with a substantially higher risk of colorectal adenoma. In 2 randomized controlled trials (RCTs), a low fat diet did not reduce the recurrence of colorectal adenomas (111, 112). In a smaller trail in Australia, a combination of low fat and wheat bran reduced the transition from smaller to larger adenomatous polyps (113). In the Women's Health Initiative (WHI) Randomized Controlled Dietary Modification Trial, a low fat diet did not reduce the incidence of invasive carcinoma (114).

Dietary fats are postulated to promote bile acid synthesis by the liver, ultimately increasing their concentrations in the colon. The colonic bacteria convert these compounds into metabolites that are toxic to the colonic mucosa and promote carcinogenesis (107).

Red and Processed Meats

Based on the findings of a group of 22 scientists from 10 countries who conducted an analysis of more than 800 observational epidemiological studies on cancer (including 14 cohort, and 15 case-controls on the association of red meat consumption with CRC; and 18 cohort, and 9 case-controls on the association of processed meat consumption with incident CRC), processed meats are classified as group 1 carcinogens for CRC, and red meat as group 2A carcinogens (115). The Working Group found a statistically significant dose-

response association between consumption of red and processed meats with risk of CRC in 10 cohort studies (17% higher risk per 100 g per day of red meat (95% CI: 1.05, 1.31), and an 18% higher risk per 50 g per day of processed meat (95% CI: 1.10, 1.28).

Consumption of red, or processed meats is also associated with a higher risk of incident colorectal adenomas. In a meta-analysis of 19 case-control, and 7 cohort studies, Aune et al. (116) found a non-linear, statistically significant association of red meat (p value <0.01), and processed meat consumption (p value = 0.01) with risk of colorectal adenomas.

It is hypothesized that the associations of meat intakes with carcinogenesis may be related to the heme content in red meats, and the nitrosyl heme content in processed meats which catalyze the formation of Apparent Total N-nitroso Compounds (ATNC), and promote lipid peroxidation (117). The ATNC lead to DNA damage and adduct formation, and ultimately mutations in the K-*ras* and p53 proto-oncogenes, both of which are found in CRC (117). Lipid peroxidation products are associated with DNA adduct formation, and *APC* gene mutations (117). Meats cooked at high temperatures are also a source of heterocyclic amines (HCAs), and poly aromatic hydrocarbons (PAHs) that may be involved in DNA damage and colorectal carcinogenesis (107).

Fruits and Vegetables

Inspite of some conflicting evidence, a high intake of fruits and vegetables is more consistently associated with a lower risk of CRC in epidemiologic studies than any other dietary factor. Compared to non-vegetarians, vegetarian dietary patterns are associated with a lower risk of CRC (118). In 35 case-control studies, a high intake of fruits and vegetables is associated with substantially lower risk of CRC (107). In a pooled analysis of 14 cohort studies, Koushik et al.(119) found eating more than 800 g of fruits and vegetables daily (vs. 200 g) was associated with a lower risk for distal CRC. In a meta-analysis of 19

cohort studies, Lee et al. (120) found a weak, but statistically significant inverse association (RR 0.92; 95% CI:0.86, 0.99). However, in two large prospective cohort studies, the NHS (109) and the HPFS (110) no association was found. A high fruits and vegetables diet did not reduce the incidence of recurrent colorectal adenoma in the Polyp Prevention Trial (112), or incidence of invasive CRC in the WHI trial (114).

Diets with high contents of fruits, and vegetables are rich in potentially anticarcinogenic compounds, and are postulated to improve systemic inflammation, and oxidative balance through multiple mechanisms, including, but not limited to induction of detoxification enzymes, inhibition of nitrosamine formation, binding of carcinogens in the gut etc. all of which are ultimately associated with a lower risk of colonic neoplasia (107).

Dietary Fiber

Although results from epidemiologic studies on the association of fiber with risk of colorectal neoplasia are mixed, increased fiber intake is generally accepted as being associated with a lower risk of colorectal neoplasia. Dietary fiber is associated with a lower risk of CRC in several prospective studies (121-125) . In a pooled analysis of 13 prospective cohort studies, Park et al. (126) found a statistically significant, inverse association of dietary fiber intake with risk of CRC, (pooled RR = 0.84; 95% CI: 0.77, 0.92), but the association was diminished after adjusting for other dietary factors (pooled multivariate RR = 0.94; 95% CI: 0.86, 1.03). In a meta-analysis by the World Cancer Research Fund, a 10g/day increase in dietary fiber was associated with a 10% lower risk of CRC (127, 128). No statistically significant inverse associations were found in the NHS (109), or in the IWHS (129). A low fat, high fiber, and high fruits and vegetables diet did not reduce the incidence of CRC in the WHI (114). Fiber supplementation also did not reduce the incidence of colonic adenomas in 3 other RCTs (113, 130, 131). In a systematic review of 5 RCTs with 4,349

participants, Asano et al. concluded that increased dietary fiber intake did not reduce the incidence, or recurrence of adenomas within a 2 – 4 year follow-up period (132).

Dietary fiber as a single entity that independently lowers the risk of neoplasia may be misleading, and that not just increased fiber, but the type of fiber is also important (107).

Plausible mechanisms to explain the association of fiber intake with a lower risk of CRC include increased stool bulk, dilution of carcinogens in the colonic lumen, reduced gastrointestinal transit time which decreases contact time with the colonic mucosa, and fermentation of fiber by colonic microflora to short chain fatty acids (SCFAs) such as butyrate, acetate, and propionate (128, 133). SCFAs play a key role in regulating homeostasis in the gut, and maintaining epithelial integrity (133).

Folic Acid and Folate

Results from epidemiologic studies suggest that intake of folic acid is associated with a lower risk of CRC. In at least 5 case-control, and 5 cohort studies, including the NHS (109), HPFS (110) and the IWHS (72), folate is found to be associated with a lower risk of CRC. Total folate intake is also statistically, significantly inversely associated with risk of colorectal adenoma (OR 0.68; 95% CI: 0.60,0.78) (99). However, in 2 RCTs, folic acid did not reduce the incidence of recurrent adenomas.(134, 135)

The molecular mechanisms that are hypothesized to be involved in colorectal carcinogenesis in relation to folate depletion include disruption of DNA repair, altered methylation of DNA and RNA, ultimately leading to disruption of DNA integrity, alteration of gene expression, and increased DNA damage (136).

Calcium

Higher total calcium intakes are consistently, modestly inversely associated with colorectal neoplasms in numerous observational epidemiologic studies, although direct

associations are also reported in others (107, 137, 138); but the evidence is favor of a lower risk for colonic neoplasia. Calcium supplementation effectively reduced adenoma recurrence in clinical trials (139, 140). In a meta-analysis of 3 RCTs trials (141), that investigated the efficacy of calcium in reducing adenoma recurrence, the incidence of recurrent adenoma(s) was statistically, significantly reduced among participants randomized to calcium (RR 0.80; 95% CI 0.68, 0.93). The effects of calcium may vary with an individual's genotype for the vitamin D receptor (142), and/or having normal levels of vitamin D (143).

There is strong biological plausibility for protection against CRC by calcium (107). Calcium directly binds to bile acids, in the bowel lumen, rendering them insert, thus inhibiting their proliferative and carcinogenic effects on the colonocytes (144). Other proposed mechanisms include direct effects on the cell cycle, and modulation of the APC colon carcinogenesis pathway (145).

Hormone Replacement Therapy

Use of postmenopausal hormone replacement therapy (HRT) (both combined estrogen plus progestin, and unopposed estrogen) is associated with a lower risk of colorectal adenoma and CRC in several observational studies (146-153).

In a meta-analysis of 12 case-control, 11 cohort studies, one case series, and one RCT, ever use of HRT was associated with a statistically significant 12% lower risk of colon cancer (RR 0.88; 95% CI: 0.80, 0.97); no association was found for rectal cancer (154). In a meta-analysis of 18 studies that included 8 case-control, and 10 cohort studies, Grostein et al. (155) found statistically significant lower risks of colon, (RR 0.80; 95% CI: 0.74, 0.86) and rectal cancers (RR 0.81, 95% CI: 0.72,0.92) among ever users of HRT. In a meta-analysis of 8 case-control, 8 cohort studies, and 4 RCTs, Lin et al. (156)found statistically significant

lower risks of CRC among ever-users of both combined HRT (RR 0.74; 95% CI: 0.68, 0.81), and estrogen replacement alone (RR 0.79; 95% CI: 0.69, 0.91), and among current estrogen users (RR 0.70; 95% CI: 0.57, 0.85)

In the follow-up to the clinical trial, Heart and Estrogen/Progestin Replacement Study (HERS), HERS II, HRT use did not reduce the incidence of colon cancer in the 2.7-year follow-up period (157) However, in the WHI trial, after 5.2 years of follow-up, HRT use (combined estrogen and progesterone, but not estrogen alone) substantially reduced the incidence of CRC (Hazard ratio [HR] 0.63; 95% CI: 0.43, 0.92) (158).

HRT may lower the risk of colorectal neoplasia by reducing the likelihood of hypermethylation of the ER gene (151). Another less popular proposed mechanism is the bile-acid hypothesis: secondary bile acids produced by the colonic bacteria are toxic to colonocytes, HRT use decreases the concentrations of these potential carcinogens in the bowel lumen (154).

Aspirin and other NSAIDs

Multiple observational studies and large, RCTs indicate that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) strongly reduce risk for colorectal neoplasms. To date, there are over 1,800 studies that investigated the use of ASA, non-aspirin NSAIDs, and COX-2 inhibitors for prevention of colorectal adenoma and CRC (159).

Aspirin use is consistently associated with a lower risk of colorectal neoplasms in epidemiologic studies (160-165), including the NHS (166), and the HPFS (167), and in systematic reviews and meta-analyses (163, 164, 168-170). In 5 major RCTs, aspirin use reduced the incidence of sporadic, recurrent colorectal adenoma (135, 165, 171-174). In 2 RCTs, Physicians' Health Study (PHS) (175), and Women's Health Study (WHS)(176) that investigated the efficacy of aspirin for primary prevention of CRC, aspirin did not reduce

the incidence of CRC, however the duration of follow-up in the trials is thought to be insufficient to detect a beneficial effect of aspirin use on incidence of CRC.

The role of aspirin in chemoprevention of colorectal adenomas in patients with hereditary colorectal neoplasia was investigated in 2 RCTs. In the Colorectal Adenoma/Carcinoma Programme (CAPP)1 trial (177), aspirin use reduced the mean size of the largest polyps among patients with FAP, but there was no statistically significant difference between the aspirin and non-aspirin groups at the end of the trial. In the CAPP2 trial (178), aspirin did not reduce the incidence of new adenomas among patients with Lynch syndrome; however, the follow-up time in the trial was only 27 months. A secondary analysis of a 10-year follow-up of trial participants found fewer Lynch syndrome-related cancers in those on aspirin for at least 2 years (incident RR 0.42; 95% CI: 0.25, 0.72, *P* = 0.001) (179).

Results from numerous cohort, and case-control studies strongly suggest that use of non-aspirin NSAIDs is associated with a substantially lower risk of colorectal neoplasms. (159) Rostom et al. (159) conducted a systematic review of observational studies and RCTs on the chemopreventive properties of NSAIDs, including non-aspirin NSAIDs and selective COX-2 inhibitors on the incidence of colorectal adenomas, CRC, and CRC-related deaths in average-to-higher risk individuals, that included 1 cohort study on CRC-related mortality, 3 cohort studies on CRC incidence, 10 case-control studies on colorectal adenomas, and 10 case-controls studies on CRC, and 4 RCTs on incidence of colorectal adenomas. The pooled results for non-aspirin NSAID use and risk of CRC were as follows: RR 0.61; 95% CI: 0.48,0.77 for cohort studies; RR 0.70; 95% CI: 0.63,0.78 for case-control studies. For non-aspirin NSAID use and risk of colorectal adenoma the pooled results were as follows: RR

0.64; 95% CI: 0.48,0.85 for cohort studies; RR 0.54; 95% CI: 0.40,0.74 for case-control studies.

Selective COX-2 inhibitors reduced the mean number of polyps, and polyp size in 2 RCTs of patients with FAP (180) (181). In 2 RCTs of non-FAP patients with a prior history of adenomas, celecoxib reduced the incidence of recurrent adenomas (182) (183). In the APPROVe trial (184), patients with a history of adenoma(s) who were randomized to rofecoxib had a lower incidence of adenoma recurrence, particularly advanced adenomas. In a pooled analysis of the 3 RCTs, Rostom et al. (159) found a statistically significantly reduced incidence of adenoma (pooled RR 0.72, 95% CI 0.68, 0.77 for any adenoma versus RR 0.56; 95% CI, 0.42, 0.75 for advanced adenomas). Although there appears to be a consistent benefit of COX-2 inhibitors in preventing adenoma recurrence, the benefit appears to be outweighed by the risk of adverse events associated with celecoxib (including myocardial infarction, stroke and congestive heart failure) (183, 184), and rofecoxib (peptic ulcer perforation, gastrointestinal obstruction, or bleeds) (185).

The anti-neoplastic properties of non-aspirin NSAIDs were also reported from studies using experimental animal models. In more than 90% of 110 published studies of animal intestinal cancer models, NSAIDs reduced the tumor multiplicity and burden of all stages of colorectal neoplasia (186, 187). In 3 separate groups of models of Sprague-Dawley rats, Pollard et al. induced cancer using high dose carcinogens; the rats were then treated with indomethacin, and in all three models there was a reduction in the tumor load (188-190). Narisawa et al. (191) found that treatment with indomethacin in CD-Fischer rats exposed to methylnitrosourea, a carcinogen, was associated with a lower incidence of colonic tumors. Piroxicam lowered colonic tumor incidence in animal models of F344 rats (192) and reduced tumor burden in male LoBUND Sprague-Dawley rats with methylazoxymethanol

acetate (MAM) induced colonic tumors (193). Sulindac reduced tumor incidence and the number of tumors per mouse in an animal study of 1,2-dimethylhydrazine (DMH)-induced mouse colonic tumors (194).

The inhibition of carcinogenesis by aspirin was also documented in experimental rodent models (195-197). Aspirin use reduced the incidence of colonic tumors in Sprague-Dawley rats (195) and F344 rats (196) exposed to carcinogens. In another rodent model, treatment with aspirin reduced the incidence of total aberrant crypt foci (ACF) in rats exposed to DMH (197).

The anti-neoplastic effects of NSAID are biologically plausible. Several mechanisms are proposed through which NSAIDs are postulated to exert their anti-carcinogenic effects.

One of the hallmarks of epithelial cell-derived malignancies is underlying chronic inflammation of tissues. There are numerous mediators that link chronic inflammation to carcinogenesis. Chronic inflammation is characterized by an increased activity in the arachidonic acid (AA) pathway, which serves as a substrate for the production of downstream biochemical mediators that are involved in the inflammatory process (186). AA is a polyunsaturated fatty acid that serves as a substrate for the cyclooxygenase (COX) pathway, the lipooxygenase (LOX) pathway and cytochrome P450 monooxygenases (198). The 2 major pathways, the COX and LOX pathways, are implicated in inflammation and carcinogenesis. The COX pathway gives rise to prostaglandins and thromboxanes (186, 198); the LOX pathway produces leukotrienes (LTs), hydroxyl fatty acids such as hydroxyeicosatetraenoic acids (HETEs) and lipoxins. (186, 198) There are two isoforms of the COX enzyme, COX-1 and COX-2 (199, 200). COX-1 is expressed in most tissues and its functions include regulating normal cellular functions such as maintenance of the gastric mucosa, regulation of renal blood flow, and platelet aggregation (201). COX-2 is usually

undetectable in normal tissues; its expression is altered by intra- and extra-cellular stimuli (202); cytokines, mitogens, or tumor promotors can upregulate the expression of COX-2 resulting in increased levels of prostaglandin synthesis in inflamed and neoplastic tissues (203, 204). More than 80% of colon cancers in humans have increased expression of COX-2 relative to the normal adjacent colonic tissue (201). The primary mechanism of action of NSAIDs, and one of the mechanisms through which NSAIDs are thought to mediate their anti-carcinogenic effects, is inhibition of cyclooxygenase (prostaglandin synthase), thereby impairing the conversion of AA to prostaglandins, prostacyclins, and thromboxanes (205). Prostaglandins inhibit apoptosis, and immune surveillance, and are associated with tumor angiogenesis and cell proliferation (206), and therefore, by inhibiting prostaglandin synthesis via inhibition of COX enzymes, NSAIDs establish a more normal cell cycle (207). NSAIDs are also postulated to exert their anti-carcinogenic effects via induction of apoptosis. AA is involved in the conversion of sphingomyelin to ceramide, a mediator of apoptosis; through the alteration of the COX mediated pathway, NSAIDs promote apoptosis in colon cancer cells via an increase in AA (208).

In addition to the alterations in the COX pathway, NSAIDs also alter the production of metabolites in the LOX pathway. Human colon cancer cells have reduced expression of the 15-LOX enzyme, which catalyzes the conversion of colonic linoleic acid to 13-S-dydroxyoctadecadioic acid (13-S-HODE), which inhibits cellular growth and induces apoptosis. NSAIDs increase apoptosis in colon cancer cells via an increased expression of 15-LOX-1 (209). In a study of patients with FAP, those who received sulindac had a regression in polyp size and number via induction of apoptosis (not through alteration of cellular proliferation) (210). Cytokines and other pro-inflammatory mediators stimulate the production of inducible nitric oxide synthetase (iNOS), which in turn produces nitric oxide

(NO), a potent pro-inflammatory mediator that contributes to carcinogenesis (211). Inhibition of upregulation of iNOS by aspirin and salicylates via inhibition of NF-kappa-B dependent transcription, was demonstrated in an *in vitro* study (212).

There is extensive epidemiologic literature pertaining to factors that are recognized to influence the risk of CRC, however, there appear to be inconsistencies in the strengths of the associations of various risk factors with risk of colorectal adenoma or CRC. For example, the RR/OR estimates for the association of calcium intake with risk of colorectal adenoma/CRC range from 0.5 to 1.8 (213, 214); from 0.4 to 1.53, for physical activity; from 0.58 to 0.95, for high fiber intake; from 0.39 to 3.7 for total energy intake, from 0.40 to 1.0 for use of HRT etc.

Inconsistencies between epidemiologic studies may be due to many reasons, including but not limited to study design, recall bias pertaining to dietary intakes in case-control studies, environmental factors, population differences in nutrient intakes, lifestyle habits, or other underlying characteristics of a given population. However, the strengths of some of these findings suggest that NSAIDs may so mask various risk factor-colorectal neoplasm associations, that they may be undetectable among NSAID users. In stratified analyses of 3 case-control studies (41, 215, 216) the associations of known risk factors for colorectal neoplasia with CRC were found to differ by non-aspirin NSAID use. In an analysis of distal colon cancer in the NHS, and the HPFS, an inverse association of calcium intake with a lower risk of colon cancer was confined to those who did not use aspirin (217). In the Polyp Prevention Trial (218) the effect of dietary interventions in reducing adenoma recurrence was found to be different among aspirin, and non-aspirin NSAID users and non-users.

Given the strong evidence of the anti-inflammatory properties of NSAIDs, and their chemopreventive role against colorectal neoplasia, we hypothesize that regular non-aspirin

NSAID use may mask, beyond simple confounding, associations of major risk factors with colorectal adenoma, and that some of the inconsistencies in risk factor-colorectal neoplasia associations, may be explained by differential proportions of NSAID use among different study populations.

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Tables

Table 1. Selected characteristics of cases and controls in three pooled case-control studies (CPRU Study 1991-1994; MAP I Study 1994-1997; and MAP II 2002)

	Cases (n = 789)		Controls (n = 2,035)		P-Value ‡
Characteristics	**Mean (SD)**	**%**	**Mean (SD)**	**%**	
Age (y)	58.1 (9.2)		54.5 (10.9)		<0.01
Men (%)		61.1		42.8	<0.01
First degree relative with CRC (%)		16.9		17.9	0.54
Smoking status (%)					
Current		24.1		14	<0.01
Former		44.9		40	
Alcohol consumption (drinks/wk)	4.8 (8.1)		3.4 (6.8)		<0.01
Body mass index (kg/m²)	27.5 (5.1)		26.8 (4.9)		<0.01
Height (inches)	67.3 (3.7)		66.2 (3.9)		<0.01
Physical activity (METs/week) *	60.4 (56.8)		58.1 (54.1)		0.33
Dietary intakes					
Total energy (kcal/d)	2,071 (780)		1,991 (724)		0.01
% calories from fat	65.8 (32.1)		60.6 (27.8)		<0.01
% calories from saturated fat	22.5 (12.0)		20.7 (10.2)		<0.01
Dietary fiber (g/d)	21.7 (9.4)		22.0 (10.1)		0.50
Total calcium (mg/d) ¶	931 (520)		978 (531)		0.03
Total folic acid (mcg/d) ¶	412 (239)		443 (256)		<0.01
Total fruits & vegetables (servings/d)	6.0 (3.4)		6.3 (3.7)		0.02
Total red & processed meats (servings/d)	1.1 (1.0)		0.9 (0.7)		<0.01
Currently take HRT (women)		13.8		21.7	<0.01
Regularly take aspirin &/or other NSAID**		35.5		41.6	<0.01
Regularly take NSAID**		14.6		22.6	<0.01
Regularly take aspirin**		24.1		25.5	0.47
Oxidative balance score ‡‡	- 1.03 (5.4)		0.48 (5.6)		<0.01

Abbreviations: CRC, colorectal cancer; HRT, hormone replacement therapy; MET, metabolic equivalents of task; NSAID, nonsteroidal anti-inflammatory drugs; SD, standard deviation.

* Moderate + vigorous.

‡ From Fisher's exact test for categorical variables, two-sample test for continuous variables.

¶ Total = diet + supplements.

** ≥ once/week.

‡‡ See definition in text; a higher oxidative balance score represents higher antioxidant relative to pro-oxidant dietary and lifestyle exposures.

Table 2. Multivariable-adjusted associations of risk factors with incident, sporadic, colorectal adenoma in three pooled case-control studies (CPRU Study, 1991-1994; MAP I study 1994-1997; and MAP II Study, 2002)

	Pooled analysis (n = 2,824)			
Risk factors†	**No. of Cases**	**No. of Controls**	**OR***	**95% CI**
Age quartiles (years)				
1 (≤ 47)	101	552	1.00	Referent
2 (48 - 55)	187	491	2.12	1.60, 2.82
3 (56 - 63)	246	508	2.70	2.04, 3.56
4 (≥ 64)	255	484	3.45	2.60, 4.57
P_{trend}◊			*< 0.01*	
Sex				
Female	307	1,164	1.00	Referent
Male	482	871	0.98	0.62, 1.54
First degree relative with CRC (%)				
No	656	1,671	1.00	Referent
Yes	133	364	1.05	0.83, 1.32
Smoking status				
Never	190	284	1.00	Referent
Former	245	938	1.35	1.10, 1.65
Current	354	813	2.68	2.09, 3.44
P_{trend}◊			*< 0.01*	
Alcohol consumption				
Nondrinker	328	890	1.00	Referent
Low	190	597	0.84	0.67, 1.04
High	271	548	1.24	1.00, 1.53
P_{trend}◊			*< 0.01*	
Body mass index (kg/m^2)				
Normal weight (18.5 - 24.9)	244	799	1.00	Referent
Underweight (< 18.5)	11	22	1.36	0.62, 3.00
Overweight (25.0 - 29.9)	324	775	1.16	0.95, 1.43
Obese (≥ 30)	210	439	1.59	1.26, 2.02
P_{trend}◊			*0.16*	
Height, quartiles (inches)				
1 (≤ 63.5)	156	432	1.00	Referent
2 (63.6 - 65.4)	245	647	1.00	0.78, 1.29
3 (65.5 - 69.4)	171	406	1.16	0.88, 1.52
4 (≥ 69.5)	217	550	1.40	1.08, 1.81
P_{trend}◊			*< 0.01*	
Physical activity, quartiles				
1	227	517	1.00	Referent
2	188	501	0.89	0.70, 1.14
3	181	509	0.88	0.69, 1.12
4	193	508	0.85	0.67, 1.08
P_{trend}◊			*0.27*	
Dietary Intakes				
Percent calories from total fat, quartiles				
1	182	512	1.00	Referent
2	186	506	1.09	0.82, 1.43
3	204	510	1.34	0.95, 1.89
4	217	507	1.52	0.97, 2.37
P_{trend}◊			*0.02*	
Percent calories from saturated fat, quartiles				
1	184	513	1.00	Referent
2	210	506	1.17	0.89, 1.53
3	185	509	1.12	0.80, 1.58
4	210	507	1.28	0.83, 1.95
P_{trend}◊			*0.23*	
Dietary fiber, quartiles				
1	189	512	1.00	Referent

2	218	508	1.22	0.95, 1.57
3	195	508	1.23	0.92, 1.63
4	187	507	1.25	0.89, 1.75
P_{trend}◊			*0.28*	
Total‡ calcium, quartiles				
1	212	512	1.00	Referent
2	208	506	1.01	0.78, 1.30
3	176	510	0.86	0.66, 1.13
4	193	507	0.98	0.74, 1.31
P_{trend}◊			*0.60*	
Total‡ folic acid, quartiles				
1	211	512	1.00	Referent
2	232	507	1.10	0.85, 1.43
3	171	509	0.81	0.61, 1.10
4	175	507	0.90	0.66, 1.21
P_{trend}◊			*0.22*	
Total fruits & vegetables, quartiles				
1	206	504	1.00	Referent
2	212	511	1.03	0.81, 1.32
3	185	518	0.89	0.69, 1.16
4	186	502	0.95	0.71, 1.28
P_{trend}◊			*0.63*	
Total red & processed meats, quartiles				
1	158	461	1.00	Referent
2	216	593	1.01	0.78, 1.31
3	194	463	1.04	0.78, 1.38
4	221	518	0.97	0.70, 1.34
P_{trend}◊			*0.86*	
HRT use (women)				
No	680	1,593	1.00	Referent
Yes	109	442	0.85	0.65, 1.11
NSAID use				
No	674	1,576	1.00	Referent
Yes	115	459	0.63	0.50, 0.80
Aspirin use				
No	599	1,517	1.00	Referent
Yes	190	518	0.79	0.64, 0.96
Oxidative balance score, quartiles¶				
1	297	509	1.00	Referent
2	185	509	0.65	0.51, 0.82
3	164	509	0.59	0.46, 0.76
4	143	508	0.54	0.41, 0.72
P_{trend}◊			*< 0.01*	

Abbreviations: CPRU, Cancer Prevention Research Unit; CRC, colorectal cancer; CI, confidence interval; HRT, hormone replacement therapy; MAP, Markers of Adenomatous Polyps; MET, metabolic equivalents of task; OR, odds ratio; NSAID, nonsteroidal anti-inflammatory drugs excluding aspirin.

*Odds ratios and 95% confidence intervals from unconditional logistic regression models. Covariates for all models, except as noted below, include age, sex, family history of colorectal cancer in a first-degree relative, smoking, alcohol intake, body mass index, height, physical activity, hormone therapy (among women), regular aspirin use, regular NSAID use, and total calcium, folate, dietary fiber, total energy, total fat, saturated fat, total fruit and vegetable, and total red and processed meats intakes. The model for fat does not include total saturated fat, the model for saturated fat does not include total fat, the model for dietary fiber does not include total fruits and vegetables, and the model for total fruits and vegetables does not include dietary fiber. Covariates for the model for oxidative balance score include age, sex, education, family history of colorectal cancer in a first-degree relative, regular aspirin use, regular NSAID use, hormone replacement therapy (among women), and total calcium, total vitamin D, total energy, total folate, and dietary fiber intakes.

† Quartiles for age were based on the distribution among the controls. Quartiles for physical activity were based on the study-specific distribution among the controls. Cutpoints for alcohol intake were based on the sex- and study-specific distribution among the controls and were defined as follows: low intake / high intake: ≤ 3 / > 3 drinks/week among males, and ≤ 3.5 / > 3.5 drinks /week among females in MAP 1; ≤ 3 / > 3 drinks/week among males, and ≤ 2 / > 2 drinks/week among females in MAP 2; and ≤ 5 / > 5 drinks/week among males, and ≤ 2.5 / > 2.5 drinks/week among females in CPRU. Cut-points quartiles for height were based on the sex -specific distribution among the controls, and were defined as follows: 67.4, 69.4, and 71.4 inches among men, and 62.5, 63.5, and 65.4 inches among women. Quartiles for all dietary intake variables and the oxidative balance score were based on the sex- and study-specific distribution among controls.

‡ Total = dietary + supplemental.

◊ Ptrend values (2-sided) were calculated by including the median of each quartile of each variable as a continuous variable in the multivariable models, except the model for body mass index, where the median of the underweight category was excluded.

¶ Oxidative balance score (OBS) calculated as described in Statistical Analysis section of the text; a higher OBS reflects higher antioxidant relative to pro-oxidant dietary and lifestyle exposures.

Table 3. Multivariable- adjusted associations of risk factors with incident, sporadic colorectal adenoma in three pooled case-control studies (CPRU Study, 1991-1994; MAP I Study, 1994-1997; and MAP II, 2002) stratified by regular non-aspirin NSAID use

	Regular use of non-aspirin NSAID (n = 574)				No regular use of non-aspirin NSAID (n = 2,250)			
Risk factors†	**No. of Cases**	**No. of Controls**	**OR***	**95% CI**	**No. of Cases**	**No. of Controls**	**OR***	**95% CI**
Age quartiles (years)								
1 (≤ 47)	14	132	1.00	Referent	87	420	1.00	Referent
2 (48 - 55)	31	114	2.97	1.44, 6.10	156	377	2.00	1.47, 2.73
3 (56 - 63)	41	109	4.05	1.98, 8.26	205	399	2.52	1.86, 3.41
4 (≥ 64)	29	104	3.16	1.51, 6.61	226	380	3.51	2.58, 4.77
P_{trend}◊			*<0.01*				*<0.01*	
Sex								
Female	52	314	1.00	Referent	255	850	1.00	Referent
Male	63	145	1.19	0.41, 3.47	419	726	0.94	0.56, 1.55
First degree relative with CRC (%)								
No	96	370	1.00	Referent	560	1,301	1.00	Referent
Yes	19	89	0.87	0.49, 1.54	114	275	1.09	0.84, 1.40
Smoking status								
Never	41	183	1.00	Referent	204	755	1.00	Referent
Former	54	213	0.86	0.53, 1.41	300	600	1.47	1.18, 1.80
Current	20	63	1.75	0.90, 3.41	170	221	2.91	2.22, 3.82
P_{trend}◊			*0.27*				*<0.01*	
Alcohol consumption								
Nondrinker	49	200	1.00	Referent	279	690	1.00	Referent
Low	24	144	0.66	0.38, 1.17	166	453	0.87	0.69, 1.11
High	42	115	1.41	0.85, 2.36	229	433	1.20	0.95, 1.52
P_{trend}◊			*0.08*				*0.01*	
Body mass index, (kg/m^2)								
Normal weight (18.5 - 24.9)	37	163	1.00	Referent	207	636	1.00	Referent
Underweight (<18.5)	0	2	n/a	n/a n/a	11	20	1.49	0.66, 3.33
Overweight (25.0 - 29.9)	32	148	0.73	0.41, 1.28	292	627	1.25	1.00, 1.56
Obese (≥ 30)	46	146	1.19	0.69, 2.04	164	293	1.67	1.28, 2.17
P_{trend} ◊			*0.44*				*0.06*	
Height, quartiles (inches)								
1 (≤ 63.5)	25	102	1.00	Referent	131	330	1.00	Referent
2 (63.6 - 65.4)	29	141	0.76	0.40, 1.43	216	506	1.08	0.82, 1.41
3 (65.5 - 69.4)	24	92	0.99	0.50, 1.93	147	314	1.20	0.89, 1.62
4 (≥ 69.5)	37	124	1.51	0.82, 2.80	180	426	1.39	1.05, 1.85
P_{trend} ◊			*0.10*				*0.01*	
Physical activity, quartiles								
1	35	121	1.00	Referent	192	396	1.00	Referent
2	26	107	0.91	0.50, 1.68	162	394	0.89	0.69, 1.17
3	25	110	0.88	0.48, 1.62	156	399	0.89	0.68, 1.16
4	29	121	0.94	0.52, 1.71	164	387	0.85	0.65, 1.11
P_{trend} ◊			*0.86*				*0.31*	
Dietary Intakes								
Percent calories from total fat, quartiles								
1	30	110	1.00	Referent	152	402	1.00	Referent
2	21	100	0.81	0.39, 1.67	165	406	1.14	0.85, 1.54

3	28	119	0.92	0.38, 2.21	176	391	1.42	0.97, 2.06
4	36	130	1.14	0.37, 3.49	181	377	1.57	0.96, 2.55
P_{trend} ◊			*0.72*				*0.02*	
Percent calories from saturated fat, quartiles								
1	28	99	1.00	Referent	156	414	1.00	Referent
2	27	118	0.76	0.38, 1.53	183	388	1.24	0.92, 1.67
3	29	113	0.80	0.33, 1.97	156	396	1.15	0.79, 1.67
4	31	129	0.70	0.23, 2.15	179	378	1.37	0.86, 2.18
P_{trend} ◊			*0.66*				*0.17*	
Dietary fiber, quartiles								
1	25	113	1.00	Referent	164	399	1.00	Referent
2	25	110	1.15	0.59, 2.27	193	398	1.26	0.95, 1.66
3	37	114	1.52	0.74, 3.09	158	394	1.17	0.86, 1.59
4	28	122	1.34	0.57, 3.17	159	385	1.26	0.87, 1.82
P_{trend} ◊			*0.50*				*0.34*	
Total‡ calcium, quartiles								
1	23	118	1.00	Referent	189	394	1.00	Referent
2	29	112	1.36	0.70, 2.63	179	394	0.95	0.72, 1.25
3	35	106	2.07	1.03, 4.17	141	404	0.72	0.53, 0.97
4	28	123	1.30	0.61, 2.75	165	384	0.93	0.68, 1.28
P_{trend} ◊			*0.72*				*0.42*	
Total‡ folic acid, quartiles								
1	25	117	1.00	Referent	186	395	1.00	Referent
2	36	103	1.54	0.79, 3.01	196	404	1.04	0.78, 1.38
3	33	118	1.16	0.56, 2.40	138	391	0.74	0.54, 1.03
4	21	121	0.73	0.34, 1.56	154	386	0.92	0.66, 1.28
P_{trend} ◊			*0.10*				*0.49*	
Total fruits & vegetables, quartiles								
1	23	113	1.00	Referent	183	391	1.00	Referent
2	32	112	1.62	0.86, 3.08	180	399	0.95	0.73, 1.23
3	32	124	1.39	0.71, 2.71	153	394	0.83	0.62, 1.11
4	28	110	1.38	0.65, 2.94	158	392	0.89	0.64, 1.23
P_{trend} ◊			*0.58*				*0.44*	
Total red & processed meats, quartiles								
1	27	98	1.00	Referent	131	363	1.00	Referent
2	29	131	0.82	0.43, 1.56	187	462	1.07	0.80, 1.42
3	29	108	0.89	0.44, 1.81	165	355	1.08	0.79, 1.49
4	30	122	0.70	0.31, 1.56	191	396	1.04	0.73, 1.49
P_{trend} ◊			*0.42*				*0.86*	
HRT use (women)								
No	94	909	1.00	Referent	586	1,270	1.00	Referent
Yes	21	136	0.77	0.41, 1.42	88	306	0.87	0.64, 1.18
Oxidative balance score, quartiles¶								
1	37	116	1.00	Referent	260	393	1.00	Referent
2	34	113	1.02	0.58, 1.79	151	396	0.59	0.45, 0.76
3	21	121	0.67	0.35, 1.28	143	388	0.58	0.44, 0.77
4	23	109	0.77	0.39, 1.54	120	399	0.50	0.37, 0.69
P_{trend} ◊			*0.33*				*<0.01*	

Abbreviations: CPRU, Cancer Prevention Research Unit; CRC, colorectal cancer; CI, confidence interval; HRT, hormone replacement therapy; MAP, Markers of Adenomatous Polyps; MET, metabolic equivalents of task; NSAID, nonsteroidal anti-inflammatory drugs excluding aspirin; OR, odds ratio.

*Odds ratios and 95% confidence intervals from unconditional logistic regression models. Covariates for all models, except as noted below include age, sex, family history of colorectal cancer in a first-degree relative, smoking, alcohol intake, body mass index, height, physical activity, hormone therapy (among women), regular aspirin use, and total calcium, folate, dietary fiber, total energy, total fat, saturated fat, total fruit and vegetable, and total red and processed meats intakes. The model for fat does not include total saturated fat, the model for saturated fat does not include total fat, the model for dietary fiber does not include total fruits and vegetables, and model for total fruits and vegetables intakes does not include dietary fiber. Covariates for the model for oxidative balance score include age, sex, education, family history of colorectal cancer in a first-degree relative, regular aspirin use, hormone replacement therapy (among women), and total calcium, total vitamin D, total energy, total folate, and dietary fiber intakes.

†Quartiles for age were based on the distribution among the controls. Quartiles for physical activity were based on the study-specific distribution among the controls.

Cutpoints for alcohol intake were based on the sex- and study-specific distribution among the controls and were defined as follows for low / high intake: ≤ 3 / > 3 drinks/week among males, and ≤ 3.5 / > 3.5 drinks/week among females in MAP 1; ≤ 3 / > 3 drinks/week vs. among males, and ≤ 2 / >2 drinks/week among females in MAP 2; and ≤ 5 / >5 drinks/week among males, and ≤ 2.5 / > 2.5 drinks/week among females in CPRU. Cut-points quartiles for height were based on the sex -specific distribution among the controls and were defined as follows: 67.4, 69.4, and 71.4 inches among men, 62.5, 63.5, and 65.4 inches among women. Quartiles for all dietary intake variables and the oxidative balance score were based on the sex- and study-specific distribution among controls.

‡Total = dietary + supplemental.

◊P_{trend} values (2-sided) were calculated by including the median of each quartile of each variable as a continuous variable in the multivariable models, except the model for body mass index, where the median of the underweight category was excluded.

¶ Oxidative balance score calculated as described in the Statistical Analysis section of the text.

Abstract

Multiple observational studies and large, randomized controlled trials indicate that non-steroidal anti-inflammatory drugs (NSAIDs) strongly reduce risk for colorectal neoplasms. However, the strengths of these findings suggest that NSAIDs may so mask various risk factor-colorectal neoplasm associations, that they may be undetectable among NSAID users. We investigated whether various risk factor-colorectal neoplasm associations differed by non-aspirin NSAID use using pooled data from three case-control studies of incident, sporadic colorectal adenoma conducted in Minnesota, North Carolina, and South Carolina between 1991 and 2002. Participants (n = 789 cases, 2,035 polyp-free controls) provided risk factor data prior to colonoscopy. The multivariable-adjusted odds ratios (OR) (95% confidence intervals [CI]) for those in the highest relative to the lowest quartiles of exposure, by regular non-aspirin NSAID non-use/use, respectively, were 1.57 (CI 0.96, 2.55) vs. 1.14 (0.37, 3.49) for fat, 1.37 (CI 0.86, 2.18) vs. 0.70 (CI 0.23, 2.25) for saturated fat, 0.93 (CI 0.68, 1.28) vs. 1.30 (CI 0.61, 2.75) for calcium, 0.89 (CI 0.64, 1.23) vs. 1.38 (CI 0.65, 2.94) for fruits and vegetables, 1.04 (CI 0.73, 1.49) vs. 0.70 (CI 0.31, 1.56) for red and processed meats, and 0.85 (CI 0.65, 1.11) vs. 0.94 (CI 0.52,1.71) for physical activity. For current versus never smokers, the ORs (CIs) among regular non-NSAID users/non-users were 2.91 (CI 2.22, 3.82) vs. 1.75 (CI 0.90, 3.41), and for those who were obese versus those who were normal weight, they were 1.67 (CI 1.28, 2.17) vs. 1.19 (CI 0.69, 2.04). The associations of age, height, intakes of alcohol, dietary fiber, and total folate, hormone replacement therapy, and oxidative balance score with adenoma did not substantially differ according to NSAID use.

These findings suggest that regular non-aspirin NSAID use may mask, beyond simple confounding, associations of major risk factors with colorectal adenoma, and support routinely assessing such associations stratified by regular non-aspirin NSAID use.

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer deaths in the United States (1), and there was an estimated global incidence of nearly 1.4 million new cases and 694,000 deaths in 2012 (2). Adenomas, or adenomatous polyps, are the precursor lesions of most cases of CRC (219, 220).

The risk of developing CRC is influenced by environmental (including diet and lifestyle) and genetic factors (4). Although the risk of CRC is higher among those who have an underlying genetic predisposition, an inherent genetic susceptibility is found in only a small proportion of individuals. Likewise, there is substantially higher risk among patients with inflammatory bowel diseases, but this accounts for only a small proportion of those who develop colorectal cancer. Notably, there is approximately a 20-fold variation in incidence rates globally (9, 106), with the highest incidence in industrialized nations, and the lowest in Africa and Asia (221). Migrants who move from low-risk to higher-risk countries and adopt a Western diet and lifestyle tend to acquire a higher risk of CRC within the first generation in their new country (104-106). Thus, diet and lifestyle appear to be the dominant factors that influence risk of sporadic CRC in most people.

There is extensive epidemiologic literature pertaining to factors that are recognized to influence risk for colorectal neoplasms. Some of the major risk factors that are directly associated with risk of colorectal neoplasms include a family history of CRC or colorectal adenoma(s), age, obesity, height, excessive energy intake, smoking, alcohol consumption, and dietary intakes of total fat, saturated fat, and red and processed meats (4). On the

other hand, risk of colorectal neoplasia is inversely associated with physical activity, regular use of aspirin and /or non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), use of hormone replacement therapy (HRT) in postmenopausal women, and calcium, folate, fiber, and fruit and vegetable intakes (4). However, with the exception of a few exposures, there appear to be inconsistencies in the strengths of the associations of various risk factors with risk of colorectal adenoma or CRC. For example, the relative risk (RR)/odds ratio (OR) estimates for the association of calcium intake with risk of colorectal adenoma/CRC range from 0.5 to 1.8 (213, 214), from 0.4 to 1.53 for physical activity, from 0.58 to 0.95 for fiber intake, from 0.39 to 3.7 for total energy intake, from 0.40 to 1.0 for HRT use, etc. The evidence for NSAID use is quite strong, with virtually all of over 100 observational studies finding approximately 40% lower risk; three major randomized clinical trials (RCTs) finding approximately 40% reduced adenoma recurrence; and smaller RCTs finding diminishment and even disappearance of adenomas among familial adenomatous polyposis (FAP) patients. The apparent substantial reduction in risk by NSAID use suggests that NSAID use may substantially mask, beyond simple confounding, associations of other risk factors with colorectal neoplasms.

CRC is a multifactorial disease involving the interaction of genetic and environmental factors. Environmental factors are largely modifiable, and their distributions may vary among different populations. One possible explanation for the inconsistencies in associations of various risk factors, other than NSAID use, with colorectal neoplasia may be that the associations differ by use of aspirin and other NSAIDs, the distributions of which have increased over the past 30 years and may differ between study populations.

In the stratified analyses of three case-control studies, the associations of modifiable risk factors for colorectal neoplasia with CRC were found to differ by non-aspirin NSAID use

(41, 215, 216). In an analysis of distal colon cancer in two large cohorts, the Nurse's Health Study (NHS) and the Health Professionals Follow-up Study (HPFS), Wu et al. (217) found that the inverse association of calcium intake with a lower risk of colon cancer was confined to those who did not use aspirin. In the Polyp Prevention Trial (218), dietary interventions reduced adenoma recurrence only among NSAID non-users.

Given the strong evidence of the strong anti-inflammatory properties of NSAIDs, and their strong chemopreventive capacity against colorectal neoplasia, we hypothesize that regular non-aspirin NSAID use may mask, beyond simple confounding, associations of major risk factors with colorectal adenoma, and that some of the past inconsistencies in risk factor-colorectal neoplasia associations may be explained by differential proportions of NSAID use among different study populations.

Methods

Study Design and Population

The data used for this analysis were pooled from three methodologically similar case-control studies of incident, sporadic colorectal adenomas conducted by the same principal investigator.

The detailed study protocols for all three studies were previously published. Briefly, the first study (the Cancer Prevention Research Unit [CPRU] study) was conducted as a collaboration between the University of Minnesota and Digestive Healthcare, PA (Minneapolis, Minnesota), a large, multi-clinic, private gastroenterology practice, from 1991 to 1994; the second (the first Markers of Adenomatous Polyps study [MAP I]) was conducted in community gastroenterology practices in Winston-Salem and Charlotte, North Carolina from 1994 to 1997; and the third (the second MAP study [MAP II]) was conducted at Consultants in Gastroenterology, PA, a large, private practice

gastroenterology group in Columbia, South Carolina, in 2002. The initial eligibility for study participation required that the patients be 30-74 years of age, speak English, have no contraindications for colonoscopy, and were scheduled to undergo outpatient, elective colonoscopy for screening or gastrointestinal symptoms at the gastroenterology practices. In the CPRU study there were two additional sets of participants were recruited as controls: 1) screening flexible sigmoidoscopy patients who were polyp-free upon screening flexible sigmoidoscopy and not referred for colonoscopy, and 2) community controls, who met the same eligibility criteria as the colonoscopy patients but did not undergo sigmoidoscopy or colonoscopy to confirm their polyp status at the time of the study. These community controls were randomly selected from the 1991 Minnesota State Driver's License Registry and frequency-matched on zip code, age (5-year intervals), and sex. Patients with known hereditary syndromes associated with a predisposition to colonic neoplasia, or a personal history of inflammatory bowel disease (IBD), colorectal adenoma, CRC, bowel resection, or past or prevalent cancer except non-melanoma skin cancer were excluded. Cumulatively, 3,317 patients were identified as potentially eligible for the three studies. All three studies had similar participation rates (68% to 76%).

The protocols of each study were approved by the institutional review boards at the institutions at which they were conducted: the University of Minnesota and each Digestive Healthcare colonoscopy site for the CPRU study, Wake Forest University School of Medicine for the MAP I study, and the University of South Carolina for the MAP II study. Each study participant provided written informed consent.

Data Collection

All the study participants, before undergoing colonoscopy, completed mailed questionnaires regarding demographic characteristics, personal medical history, family

history of CRC, hormonal and reproductive history (women only), self-reported anthropometrics, alcohol and tobacco use, and usual physical activity (via modified Paffenbarger questionnaires). Self-administered semi-quantitative Willett food frequency questionnaires were used to assess intakes of food and nutritional supplements over the preceding twelve months. The frequencies of aspirin and other NSAID use were assessed as the number of pills taken per week.

At the clinic visit, the completed questionnaires were collected. During colonoscopy polyp locations and in vivo shapes and sizes were documented on standardized forms. All polyps found during the colonoscopy were removed and examined histologically by one index study pathologist using the diagnostic criteria established for the National Polyp Study. For all participants who had a colonoscopy (all participants in the MAP I and II studies, and most of the participants in the CPRU study), based on the colonoscopy and pathology findings, participants were assigned final eligibility and divided into one of three groups if they underwent a complete, clean colonoscopy reaching the cecum: 1) cases were those found to have at least one adenoma, none of which contained invasive CRC; 2) a hyperplastic polyp group, which was excluded from further analysis; and 3) colonoscopy-negative controls were those who had no adenomatous or hyperplastic polyps. As noted above, in the CPRU study there were two additional sets of controls: screening flexible sigmoidoscopy patients who were polyp-free upon screening flexible sigmoidoscopy and community controls. Of the 3,317 participants who agreed to participate and met the final eligibility criteria, those who were found to have hyperplastic polyps, invasive CRC, or incident IBD, and those who left more than 10% of the food frequency as incomplete and/or had implausible total energy intakes (<600 kcal/day or >6,000 kcal/day) (n= 493)

were excluded from the final analyses, leaving 2,824 participants (n= 789 cases and 2,035 controls) for analysis.

Statistical Analysis:

Selected characteristics of the cases and controls were compared using the Fisher's exact test and the two-sample *t*-test for categorical and continuous variables, respectively.

We used multivariable, unconditional logistic regression to estimate the associations of each risk factor with incident colorectal adenoma, overall and stratified by regular (≥ once/week) non-aspirin NSAID use. Covariates/stratification variables were selected a priori based on their being established risk factors for colorectal adenoma. Total intakes of micronutrients were calculated as dietary plus supplemental intakes. A questionnaire-derived, equal-weight oxidative balance score (OBS) was calculated as previously described (222, 223), and included pro-oxidant variables (smoking status, BMI, and alcohol, saturated fat, and total iron intakes) and antioxidant variables (physical activity and total vitamin E, vitamin C, carotenoids, lutein, lycopene, vitamin E, omega-3 fatty acids, flavonoids, and glucosinolates intakes) such that a higher OBS represented higher antioxidant relative to pro-oxidant exposures.

All variables were analyzed as categorical variables, developed as follows. Sex, a family history of colorectal cancer in a first degree relative, and regular (≥ once/week) aspirin and non-aspirin NSAID use were dichotomous. Age was categorized into quartiles based on the distribution among the controls. Smoking was categorized as current, former or never. Alcohol consumption was categorized as none and low/high based on the study- and sex-specific distribution among the controls. Physical activity was categorized according to the study-specific quartiles among the controls. Height was categorized according to quartiles based on the sex-specific distributions among the controls. BMI was categorized according

to the World Health Organization (WHO) criteria as underweight (<18.5 kg/m^2), normal weight (18.5 - 24.9 kg/m^2), overweight (25.0 - 29.9 kg/m^2), and obese (≥ 30 kg/m^2). Hormone replacement therapy (HRT) use among women was categorized as never, former, and current. Total intakes of energy, total fat, saturated fat, dietary fiber, total calcium, total folate, total fruits and vegetables, and total red and processed meats were categorized according to quartiles based on the study- and sex-specific distributions among the controls. The OBS was categorized into quartiles based on the study- and sex-specific distribution among the controls.

The associations of each selected risk factor with colorectal adenoma were adjusted for (except as noted below) age, sex, family history of CRC in a first-degree relative, smoking status, alcohol consumption, BMI, height, physical activity, HRT use (in women), regular aspirin use, and dietary intakes of energy, total fat, saturated fat, dietary fiber, total calcium, total folate, total fruits and vegetables, and total red and processed meats. The model for fat did not include total saturated fat intake (and vice versa), and the model for dietary fiber did not include total fruit and vegetable intakes (and vice versa). The OBS-adenoma association was adjusted for age, sex, education, family history of CRC in a first-degree relative, regular use aspirin use, HRT use (in women), and total calcium, total vitamin D, total folate, dietary fiber, and total energy intakes.

The associations were calculated from the multivariable-adjusted logistic regression models as odds ratios (ORs) and their corresponding 95% confidence intervals (CI). For each variable with more than two categories, a P-value for trend was calculated by including in the models a continuous variable based on the category ranking for variables collected as categorical variables and the median of the quartiles of variables that were collected as

continuous variables. Differences in risk factor-colorectal adenoma associations according to regular non-aspirin NSAID use were assessed by comparing stratum specific ORs.

All analyses were conducted in SAS, version 9.4 (Institute Inc., Cary, North Carolina). All statistical tests were 2-sided, and $p<0.05$ or a 95% confidence interval that excluded 1.0 was considered statistically significant.

Results

Selected characteristics of the study participants in the pooled studies are shown in Table 1. On average, cases were approximately 4 years older, consumed more alcohol, had a higher BMI, were taller, and consumed more total energy, total fat, saturated fat, and red and processed meats. They were also more likely to be male and to smoke. Controls were more likely to take HRT (if a woman) and to regularly (≥ once/week) take an NSAID, aspirin, or both. On average, they had higher intakes of total calcium, total folic acid, and total fruits and vegetables, and a higher OBS.

As shown in Table 2, preliminary to, and for comparison with, assessing associations of major colorectal cancer risk factors with adenoma according to regular non-aspirin NSAID use, we assessed the overall associations of the major risk factors with colorectal adenoma, adjusted for non-aspirin NSAID use and each other. There were statistically significant direct associations of adenoma with age, smoking, alcohol consumption, BMI, height, and total fat intake, and statistically significant inverse associations with the oxidative balance score (OBS) and regular use of aspirin and other NSAIDs. There were no strong or statistically significant estimated associations with the other risk factors, although the estimated associations were in the hypothesized directions for a family history of colorectal cancer in a first degree relative (direct), physical activity (inverse), HRT use (inverse), and intakes of saturated fat (direct), total folic acid (inverse), and total fruits and vegetables

(inverse); whereas the direction of the estimated association for dietary fiber was opposite (direct) to that hypothesized, and the estimated associations for sex (men) and total calcium and total red and processed meat intakes were very close to the null.

The results of our primary analysis, associations of major colorectal cancer risk factors with adenoma according to regular non-aspirin NSAID use, are shown in Table 3 and can be compared with the findings in Table 2. None of the differences between strata were of significant magnitude to suggest statistically significant multiplicative interactions. However, the following patterns were noted: Among those who did not regularly take a non-aspirin NSAID, the estimated associations of multiple risk factors with colorectal adenoma tended to be stronger than those among those who did take a non-aspirin NSAID or among all participants combined (adjusted for regular non-aspirin NSAID use). These included stronger estimated direct associations of adenomas with age, family history of CRC in first degree relative, smoking, BMI, total fat intake, saturated fat intake, and total red and processed meat intake; and stronger estimated inverse associations with physical activity, total calcium intake, total fruit and vegetable intake, and the oxidative balance score. On the other hand, among those who regularly took a non-aspirin NSAID, the estimated direct associations of colorectal adenoma for men and with alcohol intake, and the estimated inverse association with HRT use tended to be stronger. Taking into account the ORs across the quantiles, there were no clear differences related to height, dietary fiber (the ORs in both strata were > 1.0), and total folic acid.

Discussion

Our findings suggest that regular non-aspirin NSAID use may mask, beyond simple confounding, associations of multiple major colorectal cancer risk factors with incident, sporadic colorectal adenoma. Such risk factors may include age, family history of CRC in a

first degree relative, smoking, BMI, physical activity, the oxidative balance score (representing a balance of antioxidant to pro-oxidant dietary and lifestyle exposures), and total fat, saturated fat, total red and processed meat, total calcium, and total fruit and vegetable intakes. To our knowledge, our study is the largest to date to examine whether inconsistencies in associations of multiple major risk factors with colorectal adenoma differ by non-aspirin NSAID use. If our findings were to be consistently replicated in other studies, it would suggest that differential proportions of regular NSAID users between study populations (in studies completed over the last 30 years and extant studies) may explain some of the inconsistencies in reported risk factor-colorectal neoplasm associations, and would support routinely assessing such associations stratified by regular non-aspirin NSAID use.

That NSAID use may mask, beyond simple confounding, associations of multiple major colorectal cancer risk factors with incident, sporadic colorectal adenoma is highly plausible. More than 80% of colon cancers in humans have increased expression of the cyclooxygenase (COX) enzyme, COX-2, relative to the normal adjacent colonic tissue (201). Upregulation of COX-2 is thought to be critical to intestinal polyposis. In an animal model for FAP, COX-2 overexpression was found in Apc $^{\Delta 716}$ knockout mice (224-226). The primary mechanism through which NSAIDs are thought to mediate their anti-carcinogenic effects is inhibition of COX-2 (205). *APC* mutations are a hallmark of FAP (205). The selective COX-2 inhibitors celecoxib and rofecoxib decreased polyp number and size in *APC* mutant mice.

In addition, strong, inverse associations of non-aspirin NSAID use with colorectal neoplasms are consistently found in observational epidemiologic studies. In a systematic review of over 1,700 studies that investigated the associations of aspirin and non-aspirin NSAID use with risk of colorectal neoplasia in average to higher-risk individuals, Rostom et

al. (159) found that in the cohort studies, the use of non-aspirin NSAIDs was associated with a statistically significant 39% lower risk of CRC (pooled RR 0.61; 95% CI: 0.48,0.77), and a statistically significant 30% lower risk of CRC in case-control studies (pooled RR 0.70; 95% CI: 0.63,0.78). Non-aspirin NSAID use was also associated with a statistically significant 36% lower risk of colorectal adenoma in cohort studies (pooled RR 0.64; 95% CI: 0.48,0.85), and an approximately 2-fold lower risk in case-control studies (pooled RR 0.54; 95% CI: 0.40,0.74).

Furthermore, COX-2 inhibitors also reduced adenoma recurrence in RCTs of patients with sporadic colorectal adenoma. In the Adenoma Prevention with Celecoxib (APC) (182) and the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) (183) trials, celecoxib statistically significantly reduced adenoma recurrence by 33% and 36%, respectively. In the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial (184), rofecoxib statistically significantly reduced adenoma recurrence by 35% in the first year, and by 24% after 3 years.

Finally, NSAIDs also substantially reduced polyps in FAP patients in RCTs. Celecoxib statistically significantly reduced the mean number of polyps by 28% (vs. 4.5% in the placebo group; P=0.003) (180), and rofecoxib statistically significantly reduced the mean number of polyps by 6.8% (vs. 28% versus a 3.1% increase in the placebo group; cumulative difference 9.9%, p = 0.004) (181). In 2 RCTs of patients with FAP, sulindac reduced the number of polyps; a near complete regression of polyps was noted in one trial ($p < 0.01$) (227) and a 44% reduction was found in the other (p = 0.014) (228).

The risk factors we assessed in this study have been extensively reported on in the literature and have been the subject of numerous systematic reviews and meta-analyses. Higher risk for colorectal neoplasms with increasing age (24-26) and having a history of a

first degree relative with colorectal cancer is well established (11-17). Cigarette smoke, which contains multiple carcinogens, is hypothesized to be an initiator of colorectal carcinogenesis, and smoking is consistently reported to be directly associated with colorectal adenoma and carcinoma (75-82). Obesity, which is associated with higher levels of inflammation and oxidative stress, is associated with higher risk of CRC in observational epidemiologic studies, the subject of systematic reviews and meta-analyses (32-35). Obesity is designated as a risk factor for several cancers, including CRC, by the World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) (36). Older age, smoking, and obesity are all associated with higher levels of markers of inflammation, such as CRP, TNFα, and IL-6 (229), which are associated with neoplastic growth, higher tumor grade, and risk of mortality in CRC patients (230-236). Higher levels of prostaglandin E_2 (198), possibly due to upregulation of COX-2 (40), are also found in obesity. On the other hand, regular physical activity is consistently associated with a lower risk of colorectal adenoma (41-49) and CRC in observational epidemiologic studies (50-52), the subject of meta-analyses (53) (54). More frequent physical activity may be associated with lower levels of systemic inflammation (55, 56), lower levels of prostaglandin E_2 (57), and higher levels of prostaglandin F_2, which decreases the rate of colonic cell proliferation (51).

Taller height is associated with a higher risk of colorectal neoplasia in observational studies (59) (47) (41). A taller stature may be associated with higher concentrations of IGF-1, which is linked to oxidative stress, cellular proliferation, and inhibition of apoptosis in genetically damaged cells (62).

Based on the extensive epidemiologic evidence (93-98), alcohol consumption is designated as a risk factor for CRC by the International Agency for Research on Cancer (IARC) (92). High intakes of alcohol, together with low dietary folate and methionine, are

thought to be associated with DNA hypomethylation, which is associated with the loss of normal regulation of proto-oncogene expression observed in colorectal adenomas and CRC (99).

The results from observational studies of the association of dietary fat intake with risk of colorectal neoplasia are not entirely consistent (107). Of at least 26 studies that investigated the association of dietary fat intake with risk of colorectal neoplasia, direct associations were found in 12 (including the NHS and the HPFS cohorts), inverse associations were found in 2, and no association was found in 15 studies, including the Seventh Day Adventists (108) and the IWHS (72). Dietary fats promote the synthesis of bile acids, which are converted by colonic bacteria into metabolites that are toxic to the colonic mucosa, damaging DNA and cell membranes and increasing inflammation, thus initiating and promoting carcinogenesis (107).

Based on the findings of more than 800 observational epidemiological studies on several cancers, including 32 cohort and 24 case-control on the associations of red and processed meats with incident CRC, IARC designated processed meats as group 1, and red meats as group 2A carcinogens (115). Red and processed meats are also associated with a higher risk of colorectal adenomas in at least 19 case-control, and 7 cohort studies (116). It is hypothesized that the heme content in red meats, and the nitrosyl heme content in processed meats promote lipid peroxidation (117) and mutagenesis.

A high intake of fruits and vegetables is consistently associated with a lower risk of CRC in epidemiologic studies. In 35 case-control studies (107), in 2 separate pooled analyses of 14 (119), and 19 cohort studies (120), statistically significant inverse associations were found. Diets high in fruits and vegetables are rich in potentially anti-

carcinogenic compounds, and are postulated to reduce systemic inflammation and improve oxidative balance through multiple mechanisms (107).

Although the results from epidemiologic studies on the association of fiber with risk of colorectal neoplasia are mixed, increased fiber intake is generally thought to be associated with a lower risk of colorectal neoplasia; although it is unclear whether total or certain types of fiber may be most relevant (107). In a meta-analysis by the World Cancer Research Fund, a 10 g/day increase in dietary fiber was associated with a 10% lower risk of CRC (127, 128). One of the plausible mechanisms for this association is fermentation of fiber by colonic microflora to short chain fatty acids (SCFAs) (128, 133) which in turn play a key role in regulating homeostasis in the gut, and in maintaining epithelial integrity (133).

Results from epidemiologic studies suggest that folic acid intake is inversely associated with CRC. In at least 5 case-control and 5 cohort studies, including the NHS (109), HPFS (110), and the IWHS (72), folate was found to be associated with a lower risk of CRC. The molecular mechanisms in relation to folate depletion that promote carcinogenesis include disruption of DNA repair, altered methylation of DNA and RNA, ultimately leading to alteration of gene expression and increased DNA damage (136).

Higher total calcium intakes are consistently, modestly inversely associated with colorectal neoplasms in numerous observational epidemiologic studies, although direct associations are also reported in others (107, 137, 138); but the evidence is favor of a lower risk for colonic neoplasia. Calcium supplementation also reduced adenoma recurrence in clinical trials (139, 140). There is strong biological plausibility for protection against CRC by calcium (107). Calcium directly binds to free fatty acids and bile acids in the bowel lumen rendering them insert, which reduces the consequent oxidative stress and inflammation in

the colon (144). Other proposed mechanisms include direct effects on the cell cycle, and modulation of the APC colon carcinogenesis pathway (145).

Use of postmenopausal hormone replacement therapy (HRT) (both combined estrogen plus progestin and unopposed estrogen) is associated with lower risk of colorectal adenoma and CRC. In a meta-analysis of 12 case-control, 11 cohort studies, one case series, and one RCT, ever use of HRT was associated with a statistically significant 12% lower risk of colon cancer (RR 0.88; 95% CI: 0.80, 0.97). HRT use did not reduce the incidence of colon cancer in the follow-up (157) to the Heart and Estrogen/Progestin Replacement Study (HERS), but substantially reduced the incidence of CRC in the follow-up to the WHI trial (hazard ratio [HR] 0.63; 95% CI: 0.43, 0.92) (158). HRT may lower the risk of colorectal neoplasia by reducing the likelihood of hypermethylation of the *ER* gene (151) and by decreasing concentrations of bile acids in the bowel lumen (154).

Although the basic science evidence for a role of oxidative stress in colorectal carcinogenesis is quite strong, the evidence for individual anti-oxidant micronutrients in lowering risk for CRC in humans is inconsistent. Oxidative stress is characterized by an imbalance of pro-oxidants to antioxidants, which results in higher levels of reactive oxygen and nitrogen species (RONS), which cause DNA and other macromolecular damage, which results in a higher levels of inflammation. Oxidative stress also is characterized by disruption of redox signaling and control (237) that may play a role in colorectal carcinogenesis by inducing protein and DNA damage and lipid peroxidation and impair intracellular signaling. To address the limitations of investigating micronutrients individually, investigators have created oxidative balances scores (OBS) to represent the aggregate effects of multiple anti- and pro-oxidant exposures (222, 223). Oxidative balance scores, constructed such that a higher score represents higher antioxidant relative to pro-

oxidant exposures, was strongly inversely associated with colorectal adenoma in a case-control study (n= 789 cases and 1,500 controls) (238) and with colorectal cancer in the American Cancer Society's prospective cohort study (239).

As noted in the above discussion, for many of the established risk factors for colorectal neoplasms, the hypothesized mechanisms involve inflammation and oxidative stress. We postulate that the contributions of the individual risk factors to inflammation are quite small relative to the anti-inflammatory effects of NSAIDs—especially non-aspirin NSAIDs—and thus that associations of risk factors that may affect risk through their contribution to inflammation with colorectal neoplasms may be particularly hard to detect among those who already have pharmacologically suppressed inflammation. This in turn suggests that combining NSAID users and non-users may attenuate associations of various risk factors with colorectal neoplasms, but does not rule out that in some cases that there may be synergistic effects.

Few studies reported on associations of the above reviewed risk factors according to NSAID use. In a case-control study (n=177 cases and 288 controls), Hauret et al. (41) found that the inverse association of physical activity with risk of colorectal adenoma was restricted to those did not regularly use non-aspirin NSAIDs (OR 0.37; 95% CI 0.25, 0.94). In another case-control study (n=1,933 cases and 2,410 controls), Slattery et al. (216) found that the inverse association of physical activity with risk of colon cancer was stronger among those who did not use NSAIDs (OR 0.6; 95% CI: 0.5 – 0.7). The findings in our study are consistent with those in these earlier studies. In a multi-center case-control study of 1,993 cases and 2,410 controls, Slattery et al. found that participants who consumed high levels of trans-fatty acids had a statistically significant 3-fold higher risk of developing colon cancer if they did not take a NSAID (OR 2.7; 95% CI: 1.8, 4.3), whereas risk was

approximately 2-fold higher risk (OR 1.7; 95% CI: 1.0, 2.7) among NSAID users (215). Similarly, in our study, high total fat intake was associated with a higher risk of colorectal adenoma among those who did not take a non-aspirin NSAID than among those who did (57% vs. 14% higher, respectively); the corresponding findings for saturated fats were 37% higher vs. 30 % lower risk. In a multivariate-adjusted analysis of distal colon cancer in 2 prospective cohorts, the NHS and the HPFS, Wu et al. (217) found that, relative to those with low intakes of calcium, among those with high intakes, the statistically significant inverse associations of calcium intake in the HPFS (RR 0.59; 95% CI: 0.46, 0.74) and in the NHS (RR 0.63; 95% CI: 0.47, 0.68) were confined to those who did not use aspirin. In a RCT calcium supplementation reduced adenoma recurrence more strongly among those who did not take aspirin or other NSAIDs than among those who did (140). Calcium was inversely associated with adenoma risk in our study only among those who did not take a non-aspirin NSAID; however, risk was estimated to be only 7% lower and not statistically significant. Hartman et al. (218) investigated the effect of a high-fiber, high-fruit and vegetable, and low fat diet on recurrence of adenomatous polyps in 1,905 participants in the multi-center Polyp Prevention Trial. The dietary intervention reduced adenoma recurrence only among those who did not take an NSAID (OR, 0.87; 95% CI 0.69, 1.09) or aspirin (OR 0.93; 95% CI 0.75, 1.15). The dietary intervention did not reduce adenoma recurrence among those who used NSAIDs (OR 1.36; 95% CI 0.98,1.90) or aspirin (OR 1.26; 95% CI 0.85, 1.87). In our study, the estimated association of total vegetable and fruit intake was inverse (11% lower) among those who did not take a non-aspirin NSAID, but not among regular users.

Our study had several limitations and strengths. The primary strengths of our study included the collection of data on multiple risk factors/potential confounding and effect

modifying variables; exposure assessment prior to colonoscopy and adenoma diagnosis, reducing the likelihood of recall bias; complete evaluation of the colon in cases and most controls, and standardized pathological verification of adenomas, minimizing outcome misclassification; and pooling of data collected in almost identical fashion from three study populations in three states.

Limitations include that, despite the overall substantial sample size, among those who regularly took a non-aspirin NSAID, the numbers of cases in the categories of several variables was relatively small. However, although the estimated associations among those who regularly took a non-aspirin NSAID, were unstable, among those who did not regularly take a non-aspirin NSAID, the estimated strengths of associations for multiple established risk factors for colorectal cancer were stronger than those estimated from the combined population, even adjusted for non-aspirin NSAID use. Other limitations include those inherent to case-control studies, such as recall error and the inability to assess temporality; however, most adenomas are asymptomatic and unlikely to affect someone's responses on questionnaires. While there was minimal outcome misclassification among the cases and controls confirmed via colonoscopy, such study participants may have been at higher risk and thus more similar to each other than would be the case in the general population (this may be particularly so in the CPRU study, which was conducted before colonoscopic screening became routine). Also, while the community controls and the sigmoidoscopy controls in the older CPRU study may have been more representative of the general population, some of them may have been undiagnosed cases. These limitations regarding the controls may have resulted in attenuated estimated associations. Other limitations include the well-known limitations of assessing diet via a food frequency questionnaire

(e.g., recall error, limited numbers of response items, etc.) and that most of the study participants were white.

In conclusion, taken together with previous literature, our findings suggest that regular non-aspirin NSAID use may mask, beyond simple confounding, associations of multiple major colorectal cancer risk factors with incident, sporadic colorectal adenoma, suggesting that differential proportions of regular NSAID users between study populations may explain some inconsistencies in reported risk factor-colorectal neoplasm associations, and support routinely assessing such associations stratified by regular non-aspirin NSAID use.

Summary, Public Health Implications, Possible Future Directions (Chapter III)

CRC is a common, lethal disease. Given the abundance of epidemiologic evidence on modifiable lifestyle and dietary risk factors, primary prevention and prevention of recurrence of colorectal neoplasms, is a possibility. However, given the inconsistencies in the strengths of associations of many of the risk factors with colorectal neoplasms, further investigations are needed to clarify the reasons for the inconsistencies.

NSAIDs are widely used worldwide, and the results of our study, along with those from previous studies suggest that the powerful anti-inflammatory effects of NSAIDs may mask various risk factor-colorectal neoplasia associations. If the findings from other—especially larger, prospective—studies are consistent with ours, it may explain the inconsistencies related to many risk factor-colorectal neoplasm associations, and facilitate further understanding of the etiology of colorectal neoplasms and how to prevent them.

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APPENDIX

Table 1: Selected Characteristics of NSAID/Asp users in pooled dataset

	Case	Control	P-Value
	(n=280)	(n=846)	
	Mean (SD) or N (%)		
Family History of CRC			
Yes	49 (17.5%)	152 (18.0%)	0.93
Sex			
Male	173 (61.8%)	328 (38.8%)	<0.01
Age (years)	59.10 (8.9)	55.62 (10.4)	<0.01
Smoking Status			
Current	57 (20.4%)	122 (14.4%)	<0.01
Former	143 (51.1%)	371 (43.9%)	
Alcohol use (drinks/week)	4.73 (8.6)	3.51 (7.3)	0.02
BMI (kg/m^2)	28.28 (5.5)	27.38 (5.3)	0.02
Height (inches)	67.45 (3.8)	65.89 (4.0)	<0.01
Physical Activity (met-hours/week)	63.22 (58.6)	63.56 (58.1)	0.93
Total Energy Intake (kcal)	2,142.2 (805.2)	1,969.2 (718.7)	<0.01
Percent calories from total fat	68.79 (33.3)	59.50 (27.7)	<0.01
Percent calories from saturated fat	23.33 (12.2)	20.19 (10.0)	<0.01
Total Dietary Fiber Intake	22.26 (9.1)	22.20 (10.3)	0.94
Total Calcium Intake (mg/day)	938.2 (471.9)	999.4 (548.1)	0.09
Total Folic Acid Intake (mcg)	448.6 (240.9)	463.8 (259.4)	0.39
Total Fruit and Vegetable Intake (servings/day)	6.05 (3.2)	6.38 (3.80)	0.18
Total Red and Processed Meat Intake (servings/day)	1.15 (1.0)	0.90 (0.8)	<0.01
HRT			
Yes	44 (15.7%)	219 (25.9%)	<0.01
OBS	- 1.02 (5.26)	0.83 (5.62)	<0.01

Table 2: Selected characteristics of NSAID/Aspirin non-users in pooled dataset

	Case	Control	P-Value
	(n=509)	(n=1,189)	
	Mean (SD) or N (%)		
Family History			
Yes	84 (16.5%)	212 (17.8%)	0.53
Sex			
Male	309 (60.7%)	543 (45.7%)	<0.01
Age (years)	57.57 (9.4)	53.67 (11.2)	<0.01
Smoking Status			
Current	133 (26.1%)	162 (13.6%)	<0.01
Former	211 (41.5%)	442 (37.2%)	
Alcohol use (drinks/week)	4.80 (7.9)	3.39 (6.5)	<0.01
BMI (kg/m^2)	27.13 (4.9)	26.44 (4.6)	<0.01
Height (inches)	67.22 (3.6)	66.38 (3.9)	<0.01
Physical Activity (met-hours/week)	58.78 (55.7)	54.19 (50.7)	0.10
Total Energy Intake (kcal)	2031.8 (764.6)	2007.1 (728.2)	0.53
Total Fat (gms)	71.34 (34.7)	68.27 (30.9)	0.07
Fat %kcal	64.21 (31.3)	61.45 (27.8)	0.07
Saturated dat %kcal	22.03 (11.9)	21.09 (10.3)	0.1
Total Dietary Fiber Intake	21.44 (9.6)	21.87 (10.0)	0.41
Total Calcium Intake (mg/day)	927.2 (545.3)	962.0 (518.4)	0.21
Total Folic Acid Intake (mcg)	391.4 (235.5)	428.2 (253.5)	<0.01
Total Fruit and Vegetable Intake (servings/day)	5.90 (3.5)	6.26 (3.7)	0.06
Total Red and Processed Meat Intake (servings/day)	1.05 (0.9)	0.93 (0.7)	<0.01
HRT			
Female - use	65 (12.8%)	223 (18.8%)	<0.01
OBS	- 1.03 (5.45)	0.24 (5.49)	<0.01

Table 3: Unadjusted associations of risk factors with incident, sporadic colorectal adenoma in pooled analysis

	Pooled Analysis (n=2,824)		
	OR	**95% Confidence Interval**	
Family History			
No	1.00	Referent	
Yes	0.93	0.75	1.16
Sex			
Female	1.00	Referent	
Male	2.10	1.77	2.48
Age (years)			
1	1.00	Referent	
2	2.08	1.59	2.73
3	2.65	2.04	3.44
4	2.88	2.22	3.74
Smoking Status			
Never	1.00	Referent	
Current	2.56	2.03	3.23
Former	1.67	1.38	2.01
Alcohol use (drinks/week)			
Nondrinker	1.00	Referent	
Low intake	0.86	0.70	1.06
High intake	1.34	1.11	1.63
BMI (kg/m^2) (WHO classification)			
Normal weight	1.00	Referent	
Underweight	1.64	0.78	3.42
Overweight	1.37	1.13	1.66
Obese	1.57	1.26	1.95
Height (inches)			
1	1.00	Referent	
2	1.05	0.83	1.33
3	1.17	0.90	1.51
4	1.09	0.86	1.39

Physical Activity (met-hours/week)

1	1.00	Referent	
2	0.86	0.68	1.08
3	0.81	0.64	1.02
4	0.87	0.69	1.09

Fat %kcal

1	1.00	Referent	
2	1.03	0.82	1.31
3	1.13	0.89	1.42
4	1.20	0.96	1.52

Saturated fat %kcal

1	1.00	Referent	
2	1.16	0.92	1.46
3	1.01	0.80	1.29
4	1.16	0.92	1.46

Total Dietary Fiber

1	1.00	Referent	
2	1.16	0.92	1.46
3	1.04	0.82	1.32
4	1.00	0.79	1.27

Total Calcium Intake (mg/day)

1	1.00	Referent	
2	0.99	0.79	1.25
3	0.83	0.66	1.05
4	0.92	0.73	1.16

Total Folic Acid Intake (mcg)

1	1.00	Referent	
2	1.11	0.89	1.39
3	0.82	0.64	1.03
4	0.84	0.66	1.06

Total Fruit and Vegetable Intake (servings/day)

1	1.00	Referent	
2	1.02	0.81	1.28
3	0.87	0.69	1.10

4	0.91	0.72	1.15
Total Red and Processed Meat Intake (servings/day)			
1	1.00	Referent	
2	1.06	0.84	1.35
3	1.22	0.96	1.56
4	1.25	0.98	1.58
NSAID Use			
No	1.00	Referent	
Yes	0.59	0.47	0.73
Aspirin Use			
No	1.00	Referent	
Yes	0.93	0.77	1.13
OBS			
1	1.00	Referent	
2	0.62	0.50	0.78
3	0.55	0.44	0.69
4	0.48	0.38	0.61
HRT			
Use	1.00	Referent	
No Use	1.11	0.86	1.45