Body composition and aspirin dose for colorectal adenoma prevention in a randomized clinical trial

Michael N. Passarelli[1], **Elizabeth L. Barry**[1], **Judy R. Rees**[1], **Leila A. Mott**[1], **Dennis J. Ahnen**, and **John A. Baron**[2,3,1,4,5]

[1]Department of Epidemiology, Geisel School of Medicine at Dartmouth, Hanover, New Hampshire;

[2]Department of Medicine, University of Colorado School of Medicine, Aurora, Colorado;

[3]Gastroenrology of the Rockies, Denver, Colorado;

[4]Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina;

[5]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, North Carolina.

Abstract

Background: Visceral adiposity is a risk factor for colorectal adenomas, and aspirin is an established chemopreventive agent. Evidence from clinical trials suggests the effectiveness of aspirin at preventing cardiovascular disease and cancer may require higher doses for higher body weight.

Methods: Body mass index, body surface area, fat-free mass, and fat mass were calculated from baseline height and weight in 1,121 participants of the Aspirin/Folate Polyp Prevention Study, a double-blind, placebo-controlled, 3×2 factorial randomized clinical trial of low-dose (81 mg/d) or high-dose (325 mg/d) aspirin and/or 1 mg/d folic acid to prevent metachronous colorectal adenomas. Participants were treated during a surveillance colonoscopy interval of approximately 3 years. Risk ratios (RR) with 95% confidence intervals (CI) for any colorectal neoplasia and high-risk adenoma (HRA, advanced or 3 adenomas) were estimated from log-linear regression.

Results: We did not find evidence to suggest aspirin dose-response differed by body composition measurements including weight alone. Among those weighing 80 kg, treatment effects for low-dose aspirin (RR for colorectal neoplasia, 0.75; CI, 0.60–0.94; RR for HRA, 0.52; CI, 0.31–0.86) and high-dose aspirin (RR for colorectal neoplasia, 0.88; CI, 0.72–1.08; RR for HRA, 0.68; CI, 0.43–1.09) were not meaningfully different than for those weighing 70–79 kg or <70 kg.

Corresponding Author: Michael N. Passarelli, Dartmouth-Hitchcock Medical Center, 1 Medical Center Dr, HB 7927, Lebanon, NH 03756 (michael.n.passarelli@dartmouth.edu).

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Disclosure of Potential Conflicts of Interest

Together with the Trustees of Dartmouth College, J. A. Baron holds a use patent, not licensed, for the chemopreventive use of aspirin for colorectal cancer.

Conclusions: Measurements of body composition calculated from height and weight did not modify aspirin treatment effects for colorectal adenoma prevention.

Impact: Aspirin dosing strategies accounting for body weight suggested in previous trials of colorectal cancer may not apply to adenomas.

Keywords

aspirin; body weight; body mass index; body surface area; colorectal adenoma; fat-free mass

Introduction

The United States Preventive Services Task Force recommends low-dose (81 mg/d) aspirin for the primary prevention of colorectal cancer (CRC) for those 50–69 years old with 10-year risk of cardiovascular disease ≥10%, and advocates more research on dosing strategies (1). In randomized clinical trials (RCTs), aspirin reduces metachronous colorectal adenoma risk by approximately 20% (2). A meta-analysis of RCTs found body weight modified the association between aspirin dose and CRC risk: 75–100 mg/d aspirin reduced risk among those weighing <70 kg, and ≥325 mg/d among those weighing <80 kg (3). We assessed aspirin treatment effects according to height, weight, and body composition measurements predicted from height and weight, in the Aspirin/Folate Polyp Prevention Study (AFPPS), a double-blind placebo-controlled RCT of 81 or 325 mg/d aspirin for the prevention of metachronous adenomas (4).

Materials and Methods

AFPPS is 3×2 factorial RCT comparing 81 and 325 mg/d aspirin to placebo and 1 mg/d of folic acid to placebo (4). Participants recruited from nine clinical centers between 1994–1998 were 21–80 years old and recently diagnosed with ≥1 colorectal adenoma. Aspirin treatment ended at a 3-year follow-up colonoscopy. We evaluated the incidence of any colorectal neoplasia ≥1 year following randomization determined by a standardized pathology review, including conventional adenomas, sessile serrated adenomas/polyps (SSA/P), or CRC. High-risk adenoma (HRA) findings were defined as ≥1 advanced adenoma (tubulovillous/villous adenomas, ≥1 cm in diameter, with high-grade dysplasia, or CRC) or ≥3 adenomas, without considering SSA/P.

Body mass index (BMI), body surface area (BSA) (5), and fat-free mass (FFM) (6) were calculated from self-reported baseline height and weight. Fat mass (FM) was calculated as weight minus FFM. Risk ratios (RR) with 95% confidence intervals (CIs) were estimated from log-linear regression with robust standard errors, adjusting for age, sex, center, and treatment assignment. Heterogeneity of RRs for aspirin according to body composition was tested using 2-df Wald tests for interactions with each dose vs placebo in intention-to-treat analyses. Secondary analyses were stratified by sex using different categories for body composition variables when appropriate. Two-sided $P \leq 0.05$ was considered statistically significant.

Results

Overall, 1,121 participants underwent randomization. Baseline characteristics by treatment assignment were previously reported, along with summaries of excellent compliance and avoidance of non-protocol non-steroidal anti-inflammatory drugs (NSAIDs) (4). Among 712 men and 409 women, mean (SD) height was 1.8 (0.1) m and 1.6 (0.1) m, respectively. The mean weight was 87.5 (14.6) kg and 71.9 (14.3) kg, respectively. A total of 1,084 participants (97%) completed the follow-up colonoscopy; among these, 470 (43%) had incident colorectal neoplasia, including 140 (13%) with HRA.

For each body composition measurement, risk of colorectal neoplasia and HRA increased comparing the highest to lowest category (Table 1). No statistically significant treatment effect modification was found (Table 2). Treatment effects for low-dose aspirin did not differ according to whether participants weighed <70 kg or 70 kg. High-dose aspirin did not, in general, result in statistically significant treatment effects, and there was no evidence to suggest greater risk reduction in those weighing <80 kg compared to 80 kg. Sex-specific effects were of similar magnitudes as overall sex-adjusted effects, but estimates were less precise (Supplementary Tables 1–4).

Discussion

Our findings did not show the dose-response pattern by weight identified by Rothwell et al. (3). We found low-dose aspirin reduced risk of colorectal neoplasia and HRA by 25% and 48%, respectively, among those weighing 80 kg, findings not meaningfully different from those weighing <70 kg. No effect modification was observed for other measurements of body composition.

Overall, AFPPS identified a statistically significant 19% reduced risk of adenomas for low-dose aspirin relative to placebo, and a non-significant 4% reduced risk for high-dose aspirin (4). A previous analysis from AFPPS reported treatment effects according to BMI, considering conventional and advanced adenomas as endpoints, but did not evaluate weight alone or other measurements of adoposity (7).

Abdominal visceral adiposity is a known risk factor for colorectal adenomas (8), but measurement requires medical imaging. We calculated FFM and FM using validated prediction equations trained on data from dual-energy x-ray absorptiometry and bioelectrical impedance analysis (6). FFM is often regarded as equivalent to lean body mass (LBM), although the former excludes lipids in the central nervous system, bone marrow, and cell membranes (accounting for ~4% difference between FFM and LBM) (6). We also calculated classical BSA, as it remains in use to dose some chemotherapies.

AFPPS had excellent follow-up and compliance, avoidance of non-protocol NSAIDs, standardized pathology, and evaluation of 2 different aspirin doses by design. Predictions from height and weight may be subject to error, but the randomized design helped balance any inaccuracies by treatment assignment. Weight-based aspirin dosing aims to maximize bioavailability while minimizing side-effects such as bleeding (3), but data from AFPPS

does not support the effectiveness of this approach for preventing metachronous colorectal adenomas.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Bibbins-Domingo K, U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2016;164:836–45. [PubMed: 27064677]

2. Cole BF, Logan RF, Halabi S, Benamouzig R, Sandler RS, Grainge MJ, et al. Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials. J Natl Cancer Inst 2009;101:256–66. [PubMed: 19211452]

3. Rothwell PM, Cook NR, Gaziano JM, Price JF, Belch JFF, Roncaglioni MC, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. Lancet 2018;392:387–99. [PubMed: 30017552]

4. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, et al. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med 2003;348:891–9. [PubMed: 12621133]

5. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 1916;17:863–71.

6. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet 2005;44:1051–65. [PubMed: 16176118]

7. Kim S, Baron JA, Mott LA, Burke CA, Church TR, McKeown-Eyssen GE, et al. Aspirin may be more effective in preventing colorectal adenomas in patients with higher BMI (United States). Cancer Causes Control 2006;17:1299–304. [PubMed: 17111262]

8. Keum N, Lee DH, Kim R, Greenwood DC, Giovannucci EL. Visceral adiposity and colorectal adenomas: dose-response meta-analysis of observational studies. Ann Oncol 2015;26:1101–9. [PubMed: 25480876]

Table 1.

Main effect of body composition measurements for risk of any colorectal neoplasia and high-risk adenoma in the Aspirin/Folate Polyp Prevention Study.

Baseline measurement	Total	Colorectal neoplasia		HRA	
		No. with endpoint (%)	RR[a] (95% CI)	No. with endpoint (%)	RR[a] (95% CI)
Height, m					
<1.70	407	161 (40)	1 (Ref)	41 (10)	1 (Ref)
1.70–1.79	371	159 (43)	0.96 (0.77, 1.20)	48 (13)	0.84 (0.52, 1.38)
1.80	304	149 (49)	1.12 (0.88, 1.42)	51 (17)	1.17 (0.69, 1.97)
Weight, kg					
<70	245	87 (36)	1 (Ref)	20 (8)	1 (Ref)
70–79	271	112 (41)	1.12 (0.87, 1.44)	39 (14)	1.39 (0.78, 2.46)
80	568	271 (48)	1.25 (0.99, 1.59)	81 (14)	1.42 (0.80, 2.54)
BMI, kg/m^2					
<25	333	124 (37)	1 (Ref)	32 (10)	1 (Ref)
25–29	507	229 (45)	1.14 (0.95, 1.36)	74 (15)	1.35 (0.91, 2.03)
30	242	116 (48)	1.23 (1.02, 1.50)	34 (14)	1.45 (0.92, 2.27)
BSA[b], m^2					
<1.90	441	162 (37)	1 (Ref)	43 (10)	1 (Ref)
1.90–1.99	204	91 (45)	1.15 (0.92, 1.44)	30 (15)	1.16 (0.70, 1.94)
2.00	437	216 (49)	1.29 (1.05, 1.57)	67 (15)	1.30 (0.84, 1.99)
FFM[c], kg					
<55	439	170 (39)	1 (Ref)	38 (9)	1 (Ref)
55–59	146	65 (45)	0.96 (0.68, 1.34)	24 (16)	1.08 (0.51, 2.26)
60	497	234 (47)	1.02 (0.75, 1.39)	78 (16)	1.23 (0.61, 2.48)
FM[d], kg					
<25	621	265 (43)	1 (Ref)	80 (13)	1 (Ref)
25–29	199	89 (45)	1.13 (0.94, 1.35)	27 (14)	1.33 (0.89, 1.98)
30	262	115 (44)	1.08 (0.90, 1.29)	33 (13)	1.21 (0.82, 1.77)

Abbreviations: BSA, body surface area; BMI, body mass index; CI, confidence interval; FFM, fat-free mass; FM, fat mass; HRA, high-risk adenoma; RR, risk ratio.

Note: Two participants were missing height, and thus excluded from the calculations of BMI, BSA, FFM, and FM.

[a] RR adjusted for age, sex, clinical center, aspirin assignment, and folic acid assignment. Endpoints were contrasted to those without colorectal neoplasia.

[b] Calculated using the method of DuBois and DuBois (5).

[c] Calculated using the method of Janmahasatian et al. (6).

[d] Weight minus FFM.

Table 2.

Aspirin treatment effect for risk of any colorectal neoplasia and high-risk adenoma according to body composition measurements in the Aspirin/Folate Polyp Prevention Study.

	Colorectal neoplasia		HRA	
Baseline measurement	**81 mg/d aspirin vs placebo RR[a] (95% CI)**	**325 mg/d aspirin vs placebo RR[a] (95% CI)**	**81 mg/d aspirin vs placebo RR[a] (95% CI)**	**325 mg/d aspirin vs placebo RR[a] (95% CI)**
Height, m				
<1.70	0.69 (0.50, 0.96)	1.00 (0.76, 1.31)	0.51 (0.24, 1.08)	0.83 (0.41, 1.67)
1.70–1.79	1.00 (0.72, 1.38)	1.13 (0.83, 1.53)	0.48 (0.21, 1.07)	1.00 (0.55, 1.82)
1.80	0.72 (0.54, 0.95)	0.83 (0.63, 1.08)	0.53 (0.29, 0.96)	0.73 (0.42, 1.28)
P-interaction	0.21	0.31	0.98	0.75
Weight, kg				
<70	0.82 (0.52, 1.29)	0.96 (0.63, 1.47)	0.81 (0.27, 2.50)	1.09 (0.37, 3.17)
70–79	0.87 (0.59, 1.26)	1.19 (0.85, 1.65)	0.38 (0.16, 0.91)	1.11 (0.62, 1.99)
80	0.75 (0.60, 0.94)	0.88 (0.72, 1.08)	0.52 (0.31, 0.86)	0.68 (0.43, 1.09)
P-interaction	0.79	0.33	0.58	0.40
BMI, kg/m^2				
<25	0.78 (0.55, 1.12)	1.03 (0.74, 1.42)	0.73 (0.32, 1.71)	1.16 (0.55, 2.47)
25–29	0.84 (0.66, 1.07)	0.94 (0.74, 1.18)	0.53 (0.30, 0.94)	0.93 (0.58, 1.50)
30	0.67 (0.47, 0.96)	0.92 (0.69, 1.22)	0.35 (0.16, 0.77)	0.46 (0.22, 0.98)
P-interaction	0.75	0.86	0.45	0.19
BSA[b], m^2				
<1.90	0.85 (0.62, 1.18)	1.06 (0.79, 1.43)	0.50 (0.24, 1.07)	0.93 (0.49, 1.75)
1.90–1.99	0.80 (0.53, 1.22)	1.11 (0.78, 1.58)	0.44 (0.15, 1.31)	1.28 (0.60, 2.75)
2.00	0.73 (0.57, 0.92)	0.84 (0.67, 1.04)	0.52 (0.31, 0.89)	0.63 (0.38, 1.03)
P-interaction	0.73	0.29	0.96	0.28
FFM[c], kg				
<55	0.80 (0.59, 1.09)	0.97 (0.73, 1.28)	0.36 (0.15, 0.85)	0.69 (0.35, 1.37)
55–59	1.01 (0.61, 1.67)	1.35 (0.85, 2.14)	0.90 (0.29, 2.85)	2.04 (0.77, 5.36)
60	0.72 (0.57, 0.91)	0.87 (0.71, 1.08)	0.52 (0.32, 0.87)	0.72 (0.45, 1.14)
P-interaction	0.47	0.24	0.44	0.14
FM[d], kg				
<25	0.82 (0.65, 1.04)	1.02 (0.83, 1.26)	0.64 (0.36, 1.11)	1.08 (0.68, 1.71)
25–29	0.71 (0.49, 1.05)	0.85 (0.59, 1.21)	0.40 (0.16, 1.00)	0.77 (0.37, 1.63)
30	0.74 (0.51, 1.07)	0.92 (0.66, 1.27)	0.38 (0.17, 0.83)	0.44 (0.19, 1.03)
P-interaction	0.78	0.64	0.49	0.19

Abbreviations: BSA, body surface area; BMI, body mass index; CI, confidence interval; FFM, fat-free mass; FM, fat mass; HRA, high-risk adenoma; RR, risk ratio.

Note: Two participants were missing height, and thus excluded from the calculations of BMI, BSA, FFM, and FM.

[a] RR from interaction between body composition measurement and aspirin assignment, adjusted for age, sex, clinical center, and folic acid assignment. Endpoints were contrasted to those without colorectal neoplasia.

[b] Calculated using the method of DuBois and DuBois (5).

[c] Calculated using the method of Janmahasatian et al. (6).

[d] Weight minus FFM.