

Supplementary Tables and Figures

Inflammation, Physical Activity, and Disease-Free Survival in Stage III Colon Cancer: CALGB/SWOG 80702 (Alliance)

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Short Title

Inflammation, Physical Activity, and Prognosis in Colon Cancer

Supplementary Table 1. Survey of recreational physical activity by type and duration

DURING THE PAST 2 MONTHS, what was your average time PER WEEK spent at each of the following recreational activities?	TIME PER WEEK									
	Zero	1–4 Min.	5–19 Min.	20–59 Min.	One Hour	1–1.5 Hrs.	2–3 Hrs.	4–6 Hrs.	7–10 Hrs.	11+ Hrs.
Walking for exercise or walking to work (including golf)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Jogging (slower than 10 minutes/mile)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Running (10 minutes/mile or faster)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Bicycling (including stationary machines)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Tennis, squash, racquetball	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Lap swimming	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Other aerobic exercises (calisthenics, ski or stair machine, etc.)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Lower intensity exercise (yoga, stretching, toning)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Other vigorous activities (e.g., lawn mowing)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Weight training or resistance exercise (including free weights or machines such as Nautilus)	Arm weights	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	Leg weights	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Supplementary Table 2. Baseline patient characteristics

Characteristic	Randomized Sample (N = 2,524)	Included Sample (N = 1,179)	Excluded Sample (N = 1,345)	P
Demographic factors				
Age, years, mean (SD)	60.9 (10.9)	60.8 (10.5)	61.1 (11.2)	0.61
Sex, n (%)				0.48
Male	1,390 (55.1)	658 (55.8)	732 (54.4)	
Female	1,134 (44.9)	521(44.2)	613(45.6)	
Race, n (%)				<0.001
White	1,997 (79.1)	973 (82.5)	1,024 (76.1)	
Black or African American	319 (12.6)	131 (11.1)	188 (14.0)	
Asian	107 (4.2)	34 (2.9)	73 (5.4)	
All others or not reported	101 (4.0)	41 (3.5)	60 (4.5)	
Hispanic or Latino, n (%)	191 (7.6)	65 (5.5)	126 (9.4)	<0.001
Clinical factors				
Extent of invasion through the bowel wall, n (%) ^a				0.10
T1 or T2	448 (18.0)	230 (19.6)	218 (16.5)	
T3	1,672 (67.0)	775 (66.1)	897 (67.8)	
T4	375 (15.0)	167 (14.2)	208 (15.7)	
Missing	29	7	22	
Nodal stage, n (%) ^b				0.57
N1	1,851 (73.3)	871 (73.9)	980 (72.9)	
N2	673 (26.7)	308 (26.1)	365 (27.1)	
Risk group, n (%)				0.46
Low (T1, T2, or T3, N1)	1,584 (63.5%)	753 (64.2)	831 (62.8)	
High (T4, N2, or both)	911 (36.5%)	419 (35.8)	492 (37.2)	
Missing	29	7	22	
Tumor location, n (%)				0.093
Left	1,172 (47.0)	576 (49.3)	596 (44.9)	
Right	1,313 (52.6)	588 (50.3)	725 (54.6)	
Multiple	11 (0.44)	5 (0.43)	6 (0.45)	
Missing	28	10	18	
ECOG performance status, n (%) ^c				0.23
0	1,795 (71.1)	852 (72.3)	943 (70.1)	
1-2	729 (28.9)	327 (27.7)	402 (29.9)	
Low dose aspirin use, n (%)	542 (21.5)	277 (23.5)	265 (19.7)	0.021
Randomization groups				
Chemotherapy, n (%)				0.30
3 Months	1,263 (50.0)	603 (51.1)	660 (49.1)	
6 Months	1,261 (50.0)	576 (48.9)	685 (50.9)	
Pharmacotherapy, n (%)				0.52
Celecoxib	1,263 (50.0)	598 (50.7)	665 (49.4)	
Placebo	1,261 (50.0)	581 (49.3)	680 (50.6)	

^aT1 indicates tumor has grown into the submucosa; T2, growth into the muscularis propria; T3, growth through the muscularis propria and into the subserosa; T4, growth into the surface of the visceral peritoneum or into or has attached to other organs or structures.

^bN1 indicates 1 to 3 lymph nodes tested positive for cancer (or for this table, N1c: tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional lymph node metastases); N2, four or more lymph nodes tested positive for cancer.

^cPerformance status: 0 indicates fully active; 1, restricted in physically strenuous activity but ambulatory and able to carry out light work; and 2, ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours.

Supplementary Table 3. Spearman correlations (ρ) between inflammatory biomarkers

	hs-CRP	IL6	sTNF-αR2
hs-CRP	$\rho=1.00$	—	—
IL6	$\rho=0.55$ P<0.001	$\rho=1.00$	—
sTNF-αR2	$\rho=0.31$ P<0.001	$\rho=0.41$ P<0.001	$\rho=1.00$

Supplementary Table 4. Inflammatory biomarker tertile values

	hs-CRP, mg/L	IL6, pg/mL	sTNF-αR2, pg/mL
Tertile 1	≤ 1.572	≤ 2.756	≤ 2519.32
Tertile 2	1.575–4.234	2.758–5.127	2520.48–3324.77
Tertile 3	≥ 4.246	≥ 5.143	≥ 3326.6

Supplementary Table 5. Inflammatory biomarker values by physical activity status

	hs-CRP, mg/L	IL6, pg/mL	sTNF-αR2, pg/mL
Insufficiently Physically Active (<9 MET), Median (IQR)	2.99 (1.41, 6.48)	4.07 (2.53, 6.94)	3047 (2480, 3826)
Sufficiently Physically Active (\geq 9 MET), Median (IQR)	2.16 (1.01, 4.50)	3.32 (2.10, 5.45)	2688 (2193, 3387)
Difference in medians (95% CI)	-0.66 (-0.96, -0.39)	-0.67 (-0.96, -0.40)	-361 (-468, -256)
P	<0.001	<0.001	<0.001

Difference in medians and p values were calculated by the Hodges-Lehmann location of shift, and Wilcoxon rank sum test, respectively.

Supplementary Table 6. Association of disease-free survival endpoint with individual inflammatory biomarkers and physical activity status

Inflammatory Burden and Physical Activity Status	3-y DFS Rate (95% CI)^{a,b}	3-y Risk Difference (95% CI)^{a,c}	P^c	Hazard Ratio (95% CI)^a	P
Low hs-CRP					
Sufficient Physical Activity	87.4 (82.0, 91.0)	0.0–Reference	—	1.00–Reference	—
Insufficient Physical Activity	81.8 (74.9, 86.8)	–5.6 (–12.8, 1.6)	0.12	1.49 (0.96, 2.32)	0.08
Intermediate hs-CRP					
Sufficient Physical Activity	82.2 (75.6, 87.1)	–5.2 (–12.3, 1.9)	0.15	1.45 (0.93, 2.25)	0.10
Insufficient Physical Activity	75.7 (68.3, 81.4)	–11.7 (–19.1, –4.3)	0.002	2.07 (1.38, 3.10)	<0.001
High hs-CRP					
Sufficient Physical Activity	86.5 (79.9, 90.7)	–0.9 (–8.1, 6.3)	0.80	1.07 (0.65, 1.76)	0.79
Insufficient Physical Activity	76.8 (70.0, 82.5)	–10.6 (–17.5, –3.7)	0.004	1.95 (1.30, 2.93)	0.001
Low IL6					
Sufficient Physical Activity	87.9 (82.4, 91.5)	0.0–Reference	—	1.00–Reference	—
Insufficient Physical Activity	80.1 (73.0, 85.5)	–7.8 (–15.1, –0.5)	0.034	1.71 (1.10, 2.68)	0.020
Intermediate IL6					
Sufficient Physical Activity	86.1 (80.2, 90.3)	–1.8 (–8.5, 4.9)	0.60	1.16 (0.72, 1.86)	0.55
Insufficient Physical Activity	77.4 (70.2, 82.9)	–10.5 (–17.7, –3.3)	0.005	1.99 (1.30, 3.04)	0.002
High IL6					
Sufficient Physical Activity	81.7 (74.3, 86.5)	–6.2 (–13.8, 1.4)	0.10	1.57 (0.99, 2.49)	0.060
Insufficient Physical Activity	77.0 (70.3, 82.5)	–10.9 (–17.8, –4.0)	0.003	2.03 (1.34, 3.06)	<0.001
Low sTNF-α2,					
Sufficient Physical Activity	85.9 (80.1, 90.0)	0.0–Reference	—	1.00–Reference	—
Insufficient Physical Activity	80.1 (72.6, 85.6)	–5.8 (–13.4, 1.8)	0.12	1.47 (0.95, 2.26)	0.08
Intermediate sTNF-α2,					
Sufficient Physical Activity	85.7 (79.4, 90.0)	–0.2 (–7.1, 6.7)	0.95	1.02 (0.64, 1.62)	0.93
Insufficient Physical Activity	78.7 (71.9, 83.8)	–7.2 (–14.3, –0.1)	0.046	1.58 (1.06, 2.37)	0.030
High sTNF-α2,					
Sufficient Physical Activity	84.6 (78.0, 88.9)	–1.3 (–8.8, 6.2)	0.73	1.11 (0.70, 1.74)	0.66
Insufficient Physical Activity	76.0 (69.2, 81.7)	–9.9 (–16.9, –2.9)	0.006	1.81 (1.23, 2.67)	0.002

Abbreviations: DFS, disease-free survival; CI, confidence interval; y, year.

^aAdjusted for sex, extent of invasion through the bowel wall, nodal stage, prudent dietary pattern (time-varying), chemotherapy randomization, and pharmacotherapy randomization. Continuous covariates were modeled linearly, and categorical covariates were modeled using the categories presented in Table 1.

^bCovariates for predicting disease-free survival rates were set to the mean of the study population for continuous variables and most common category for categorical variables.

^c95% confidence intervals and p values were calculated via test of proportions.

Supplementary Table 7. Association of overall survival endpoint with individual inflammatory biomarkers and physical activity status

Inflammatory Burden and Physical Activity Status	5-y OS Rate (95% CI)^{a,b}	5-y Risk Difference (95% CI)^{a,c}	P^c	Hazard Ratio (95% CI)^a	P
Low hs-CRP					
Sufficient Physical Activity	93.4 (89.2, 95.9)	0.0–Reference	—	1.00–Reference	—
Insufficient Physical Activity	89.7 (84.2, 93.4)	–3.7 (–9.2, 1.8)	0.19	1.60 (0.88, 2.88)	0.12
Intermediate hs-CRP					
Sufficient Physical Activity	89.6 (84.3, 93.2)	–3.8 (–9.3, 1.7)	0.18	1.61 (0.90, 2.91)	0.11
Insufficient Physical Activity	85.1 (78.3, 90.1)	–8.3 (–14.2, –2.4)	0.006	2.38 (1.38, 4.08)	0.002
High hs-CRP					
Sufficient Physical Activity	92.4 (86.7, 95.4)	–1.0 (–6.5, 4.5)	0.72	1.17 (0.60, 2.28)	0.64
Insufficient Physical Activity	86.4 (80.6, 90.9)	–7.0 (–12.4, –1.6)	0.015	2.16 (1.26, 3.70)	0.005
Low IL6					
Sufficient Physical Activity	93.9 (89.6, 96.4)	0.0–Reference	—	1.00–Reference	—
Insufficient Physical Activity	87.3 (81.0, 91.7)	–6.6 (–12.4, –0.8)	0.024	2.17 (1.19, 3.96)	0.012
Intermediate IL6					
Sufficient Physical Activity	92.3 (87.8, 95.1)	–1.6 (–6.7, 3.5)	0.53	1.28 (0.66, 2.47)	0.46
Insufficient Physical Activity	84.9 (78.1, 89.9)	–9.0 (–14.8, –3.2)	0.003	2.61 (1.47, 4.64)	0.001
High IL6					
Sufficient Physical Activity	89.4 (83.0, 93.2)	–4.5 (–10.4, 1.4)	0.12	1.79 (0.95, 3.36)	0.07
Insufficient Physical Activity	88.7 (83.5, 92.6)	–5.2 (–10.3, 0.0)	0.053	1.91 (1.07, 3.41)	0.03
Low sTNF-α2,					
Sufficient Physical Activity	93.2 (88.5, 95.8)	0.0–Reference	—	1.00–Reference	—
Insufficient Physical Activity	88.2 (81.8, 92.6)	–5.0 (–10.9, 0.9)	0.09	1.78 (0.97, 3.26)	0.06
Intermediate sTNF-α2,					
Sufficient Physical Activity	91.8 (86.9, 94.9)	–1.4 (–6.7, 3.9)	0.60	1.21 (0.63, 2.32)	0.56
Insufficient Physical Activity	87.8 (81.9, 91.9)	–5.4 (–10.8, 0.1)	0.052	1.84 (1.03, 3.29)	0.04
High sTNF-α2,					
Sufficient Physical Activity	90.8 (85.3, 94.1)	–2.4 (–8.2, 3.4)	0.40	1.37 (0.73, 2.58)	0.32
Insufficient Physical Activity	85.7 (79.7, 90.3)	–7.5 (–12.9, –2.1)	0.008	2.18 (1.24, 3.82)	0.006

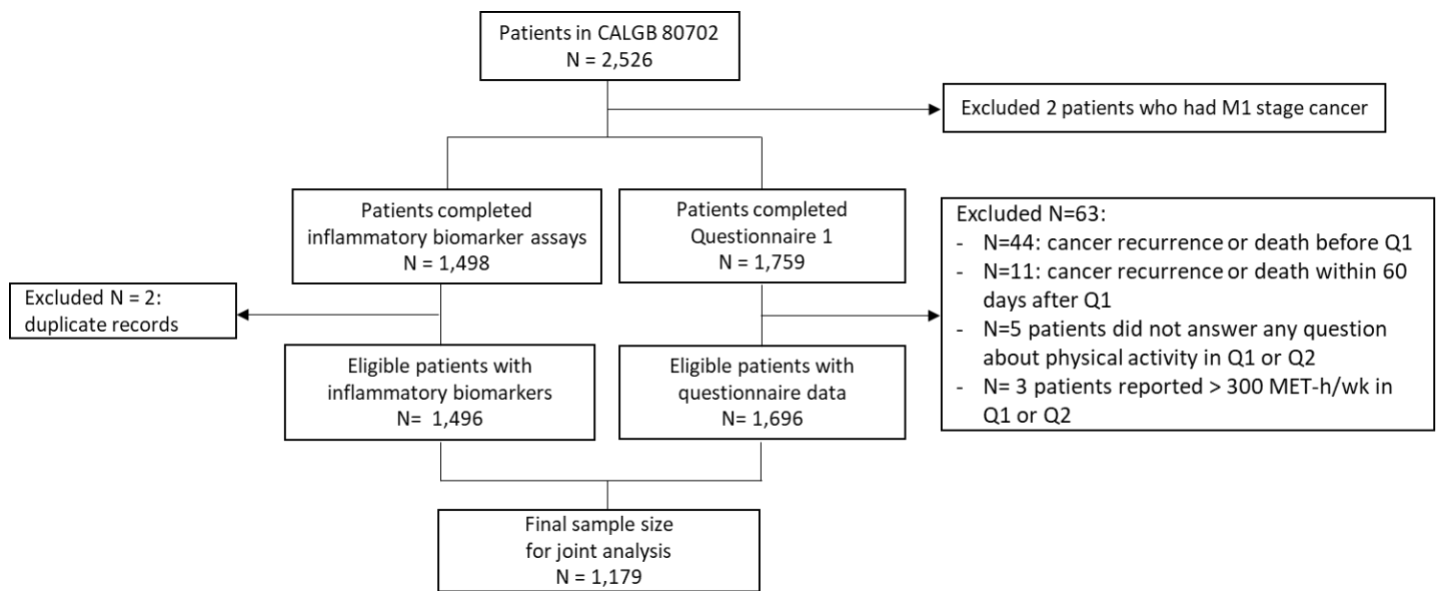
Abbreviations: DFS, disease-free survival; CI, confidence interval; y, year.

^aAdjusted for sex, extent of invasion through the bowel wall, nodal stage, prudent dietary pattern (time-varying), chemotherapy randomization, and pharmacotherapy randomization. Continuous covariates were modeled linearly, and categorical covariates were modeled using the categories presented in Table 1.

^bCovariates for predicting disease-free survival rates were set to the mean of the study population for continuous variables and most common category for categorical variables.

^c95% confidence intervals and p values were calculated via test of proportions.

Supplementary Figure 1. CONSORT Flow Diagram



Q1, physical activity questionnaire 1; Q2, physical activity questionnaire two