JNCI Cancer Spectrum (2020) 4(1): pkz096

doi: 10.1093/jncics/pkz096
First published online November 20, 2019
Article

ARTICLE

Randomized Phase II Trial of Exercise, Metformin, or Both on Metabolic Biomarkers in Colorectal and Breast Cancer Survivors

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Abstract

Background: Observational data support inverse relationships between exercise or metformin use and disease outcomes in colorectal and breast cancer survivors, although the mechanisms underlying these associations are not well understood.
Methods: In a phase II trial, stage I–III colorectal and breast cancer survivors who completed standard therapy were randomly assigned to structured exercise or metformin or both or neither for 12 weeks. The primary outcome was change in fasting insulin levels; secondary outcomes included changes in other blood-based energetic biomarkers and anthropometric measurements. Analyses used linear mixed models.
Results: In total, 139 patients were randomly assigned; 91 (65%) completed follow-up assessments. Fasting insulin levels statistically significantly decreased in all three intervention arms (−2.47 μU/mL combination arm, −0.08 μU/mL exercise only, −1.16 μU/mL metformin only, + 2.79 μU/mL control arm). Compared with the control arm, all groups experienced statistically significant weight loss between baseline and 12 weeks (−1.8% combination arm, −0.22% exercise only, −1.0% metformin only, +1.55% control). The combination arm also experienced statistically significant improvements in the homeostatic model assessment for insulin resistance (−30.6% combination arm, +61.2% control) and leptin (−42.2% combination arm, −0.8% control), compared with the control arm. The interventions did not change insulin-like growth factor–1 or insulin-like growth factor binding protein–3 measurements as compared with the control arm. Tolerance to metformin limited compliance (approximately 50% of the participants took at least 75% of the planned dosages in both treatment arms).
Conclusions: The combination of exercise and metformin statistically significantly improved insulin and associated metabolic markers, as compared to the control arm, with potential greater effect than either exercise or metformin alone though power limited formal synergy testing. Larger efforts are warranted to determine if such a combined modality intervention can improve outcomes in colorectal and breast cancer survivors.

Dysregulated metabolism is a major hallmark of all solid tumors (1). Mounting evidence demonstrates the importance of energy balance and metabolic factors in cancer development, growth, and recurrence (2–12). Multiple studies have observed

Received: July 3, 2019; **Revised:** August 19, 2019; **Accepted:** November 18, 2019

associations between high levels of circulating metabolic factors and outcomes (1,2,13–18). Similarly, observational studies have demonstrated that both breast and colorectal cancer survivors who are more physically active either before diagnosis or after diagnosis have improved outcomes (19–24). One hypothesis as to a biological mechanism associating exercise with outcomes relates to insulin and related metabolic factors driving tumor pathogenesis and progression (4,25). Indeed, several studies in colorectal and breast cancer patients suggest exercise statistically significantly lowered insulin and other factors, compared with control groups (26–30).

Metformin is a biguanide derivative approved for type 2 diabetes treatment. Metformin reduces glucose concentration leading to decline in insulin levels and insulin resistance (31), as well as activates the LKB1/AMP-activated protein kinase pathway, decreasing protein synthesis and cell growth (32). Observational studies have demonstrated that diabetics who take metformin are at lower risk than diabetics who take other agents of developing breast and colorectal cancer (33–35), and diabetics who take metformin after diagnosis may have improved response to chemotherapy (36) and lower cancer-related mortality (37–41).

Based on these observations, trials have been conducted or are underway testing the effects of exercise or metformin on circulating metabolic factors, as well as cancer-related outcomes (26,27,29,42–45). Studies to date have largely examined effects as single agents. We conducted a multicenter, randomized phase II trial for colorectal and breast cancer survivors to test the effects of combining an exercise intervention with metformin, compared with either intervention alone or with a control group on insulin, and other metabolic biomarkers, as well as weight, body mass index (BMI), and exercise measures. This trial was supported through the National Cancer Institute's Transdisciplinary Research in Cancer (TREC) program (46).

Methods

Study Population

The study was an open-label, randomized phase II trial designed to test the effect of exercise, metformin, or both interventions on fasting insulin levels in colorectal and breast cancer survivors. The original protocol was limited to individuals with stage I–III colorectal cancer who had undergone curative-intent surgery and completed adjuvant therapy (if indicated) within 2–24 months before enrollment. Participants had to engage in less than 120 minutes of exercise per week, have Eastern Cooperative Oncology Group performance status 0 or 1, random glucose less than 160 mg/dL or fasting glucose less than 126 mg/dL, no major surgery within 1 month of the start of intervention or planned surgeries within the intervention period, no evidence of metastatic disease, and not be on diabetes pharmacological therapy. The study activated at the Dana-Farber Cancer Institute in June 2011 and at Duke University Medical Center in January 2012. Because of slow accrual, the inclusion criteria were expanded to include patients with stage I–III breast cancer who completed standard treatment (concurrent hormonal therapy and/or trastuzumab were allowed). In addition, the restriction to have completed therapy within 24 months was removed. In October 2013, Duke's enrollment was discontinued because the site principal investigator changed institutions. Yale Cancer Center was activated in May 2014. Each institution's institutional review board approved the study, and informed consent was obtained from participants before enrollment. All potential participants' medical oncologist or surgeon provided medical clearance.

Study Design

Participants were randomly assigned to one of four treatment arms: exercise, metformin, exercise combined with metformin, or wait-list control. Although the initial study design included a 6-month intervention, after 2 patients enrolled, the protocol was amended to a 12-week interventions. The control group was offered consultation with an exercise trainer after the 12-week measurements. Random assignment was performed using a random permuted block design of fixed block sizes with stratification by BMI (less than 30 vs 30 or greater kg/m^2), cancer type, and sex.

Exercise Intervention

The exercise intervention consisted of in-person structured aerobic sessions, administered twice a week, and additional at-home aerobic activity weekly. Exercise training sessions began with a 5-minute warm-up followed by 30–60 minutes of moderate-intensity exercise, followed by a 5-minute cool down and 5–10 minutes of static stretching. Participants gradually increased exercise duration and intensity over the 12-week intervention, under the guidance of the trainer. The weekly aim was for a 10–20% increase in total exercise duration until participants reached the goal of 220 minutes of moderate-intensity exercise per week. Trainers used heart rate monitors during supervised sessions so that patients learned to recognize moderate-intensity exertion.

Metformin Intervention

Metformin treatment initiated at 850 mg daily for 2 weeks, increasing to 850 mg twice daily in participants tolerating initial dosing. Participants with poor tolerance continued at 850 mg daily for an additional week and then adjusted to twice a day on discussion with investigators. If dose escalation was not tolerated, participants remained on 850 mg daily for the 12-week intervention.

Measurements and Outcomes

Demographic data, disease and treatment information, and baseline physical activity information were collected via interview and/or review of medical records. Participants underwent a series of anthropometric measurements at study enrollment and at completion of the 12-week study period by study staff who were blinded to group assignment.

Patients completed a 7-day physical activity recall interview at baseline and 12 weeks, measuring duration and intensity of exercise performed, as well as time spent sleeping and engaging in other sedentary activities (47–49). Participants underwent the 6-Minute Walk Test at baseline and 12 weeks, a validated measure of functional capacity evaluating the distance an individual can walk over a flat, indoor surface in 6 minutes (50).

Fasting (greater than 12 hours) blood was drawn at baseline and 12 weeks. Insulin resistance was calculated by the homeostatic model assessment (HOMA), with the following formula: HOMA = [insulin (μU/mL) x glucose (mg/dL)]/405. Insulin and leptin were measured using a radioimmunoassay method.

Insulin-like growth factor–1 (IGF 1) was assessed using an enzyme-linked immunosorbent assays. All assays were carried out by laboratory personnel blinded to participant assignment. Each sample was assayed in duplicate for each analyte. The correlations between replicates exceeded 0.95. The mean intra-batch coefficients of variation calculated from the quality-control samples were 2.5%, 3.0%, 3.1%, 2.8%, and 2.3% for glucose, insulin-like growth factor binding protein–3 (IGFBP 3), IGF 1, insulin, and leptin, respectively.

Sample-Size Justification and Statistical Analysis

Baseline characteristics are presented as median and interquartile range (IQR) or frequency and percent age. All available outcome data were analyzed in an intention-to-treat analysis with a mixed model that was adjusted for baseline level, BMI, sex, cancer type, and study site. The main effect of each intervention, which is the difference in the least squares means from baseline to 12 weeks, was presented with the standard error. One-sided *P* was also performed to test if the changes in treatment arms were greater than in the control group, or if the change in combined arm was greater than exercise only or metformin only. To have an overall significance level of 5%, the Holm method was used to split alpha for multiple comparison testing (51). The trial was powered for the primary endpoint of change in insulin levels for a sample size of 200 participants. We assumed a between-subject SD of 4 μU /mL in all four arms (27). As such, the study had 94% power to detect a difference of 3.0 μU /mL between the control and the combination arms with a significance level of 0.0167, 87% power to detect a difference of 2.5 μU /mL between control and supervised exercise with a significance level of 0.025, and 34% power to detect a difference of 1 μU/mL between control and metformin alone with alpha of 0.05, using one-sided two-sample Student *t* tests. Because of slow accrual and end in grant funding, we ultimately enrolled 139 patients. Post hoc statistical assumptions, the accrued cohort led to 83% power to detect a difference of 3.0 μU /mL between control and combination arms with a statistical significance level of 0.0167, 73% power to detect a difference of 2.5 μU /mL between control and supervised exercise with a significance level of 0.025, and 27% power to detect a difference of 1 μU/mL between control and metformin alone with alpha of 0.05, using one-sided two-sample Student *t* tests. We tested synergistic effects of the two treatments by including a three-way interaction term for time (baseline/12 weeks) $\times$ metformin $\times$ exercise in the mixed models.

Results

Cohort Characteristics

A total of 139 participants were randomly assigned between September 2011 and December 2015 (Figure 1). Ninety-one participants (65%) completed study requirements, including assigned intervention through 12 weeks and follow-up measurements. Reasons for study discontinuation included adverse events (primarily metformin toxicity), time commitment, withdrawal of consent, loss to follow-up, physician decision, or unrelated medical issues. Attrition was greater in the metformin arm (43%) and usual care arm (41%) than in either arm with an exercise component (29% in the combination arm and 26% in the exercise-only arm). Table 1 represents baseline characteristics by treatment arm.

Compliance With Interventions and Toxicities

Participants randomly assigned to exercise and metformin increased exercise by 167 minutes/week from baseline, and participants in the exercise-only group increased by 140 minutes/week, both statistically significantly greater than increases in the control and metformin-alone groups (30 and 27 minutes/week, respectively; $P < .0001$ for both exercise arms, compared with control and with metformin only, Table 2).

Metformin adherence was assessed through self-report, with confirmation by pill count, and exercise compliance by completion of required sessions (Table 3). Adherence to the metformin intervention was moderate, with approximately 50% of participants taking at least 75% of planned dosages in both treatment arms.

No clinically meaningful exercise intervention–associated complications were reported. Toxicities for metformin were as anticipated (Table 4). Gastrointestinal toxicities were most prominent, with 40% of patients experiencing any grade diarrhea in the combination arm and 23% in the metformin-only arm. Although grade 3 toxicities were uncommon, 50% of patients who dropped out of the combination arm and 60% who dropped out of metformin-only arm experienced at least grade 1 toxicity related to metformin.

Compliance and toxicities with exercise and metformin (alone or in combination) did not differ by cancer type. There were no statistically significant differences in baseline characteristics for those who completed intervention and measurements per protocol and those who did not.

Effects on Insulin and Metabolic Biomarkers

Table 5 lists all hormonal measurements. Whereas the control group demonstrated an increase in insulin (2.79 μU/mL), all three intervention arms showed a statistically significant decrease compared with the control arm, with greatest decrease in the combination arm (−2.47 μU/mL). Insulin also decreased by −0.08 μU/mL in the exercise-only arm and -1.16 μU/mL in the metformin-only arm. The decrease in fasting insulin was statistically significantly greater in the combination arm vs the exercise-only arm ($P = .03$), but not the metformin-only arm ($P = .11$). There was no evidence that metformin and exercise had synergistic effects on biomarkers; the three-way interaction term for time $\times$ metformin $\times$ exercise was not statistically significant in mixed models ($P = .49$), albeit power was limited for this test. There was no interaction between insulin change and on going hormonal therapy usage ($P = .13$).

The HOMA for insulin resistance was statistically significantly improved for each intervention arm compared with the control arm, with a greater decrease in the combination arm. The combination arm also experienced a statistically significant decrease in leptin level vs the control arm (−5.09 vs −0.02 nanograms [ng]/mL, $P = .0002$). This change was also statistically significantly greater than either single intervention arm. There were no statistically significant differences in changes IGF 1 or in IGFBP3 between any of the intervention arms and the control arm, though there was a statistically significant difference in change in IGF between the combination arm and the exercise-only arm. The change in IGFBP 3 for the combination arm was unexpected; we tested for one or two outliers, skewing the data, but 68% of patients in this arm either had stable or decreased IGFBP 3 levels, so the results were not driven by a limited

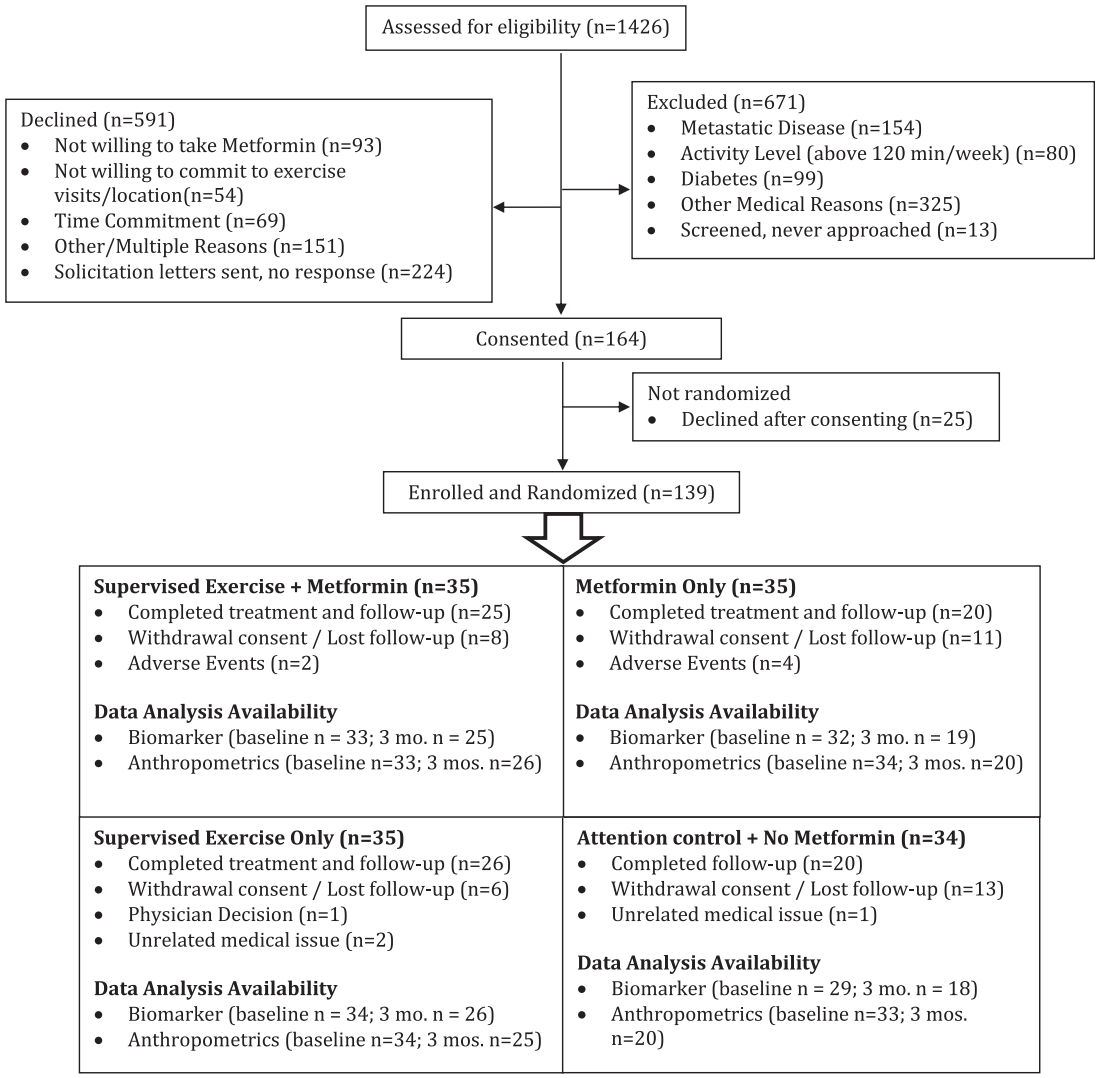

Figure 1. Consolidated Standards of Reporting Trials diagram.

number of patients and may be due to chance or an interactive effect that was unexpected.

Test for heterogeneity of the treatment effects between the two cancers types were not statistically significant for any of the biomarkers. In exploratory analyses, we did not detect any statistically significant interactions between compliance with therapy and change in biomarker levels.

There were greater effects of the interventions, particularly exercise with metformin, on insulin, glucose, HOMA, and BMI for participants with greater baseline values for each marker/measure. ($P_{interaction} < 0.05$; Supplementary Table 1, available online.)

Changes in Anthropometrics

Baseline weight, BMI, waist-to-hip ratio, and waist circumference were similar across all four arms (Table 1). All interventions led to statistically significant improvements in weight and BMI, compared with the control group ($P < .0001$, Table 5). The combination arm also statistically significantly improved waist-to-hip ratio compared with the control group (0.78% decrease vs 1.9% increase, $P = .01$). In exploratory analyses, there was a marginally statistically significant interaction between intervention compliance and change in weight ($P = .08$) and BMI ($P = .05$) for participants in the combination and metformin-only groups. Participants who had 75% or greater intervention compliance had a trend toward larger changes in weight and BMI, as compared with participants who had less than 75% compliance.

Discussion

In a cohort of 139 physically inactive, breast and colorectal cancer survivors, we found that exercise and metformin had a favorable effect on fasting insulin and other metabolic biomarkers implicated in prognosis in breast and colorectal cancer. Participants randomly assigned to any of the three intervention arms experienced a statistically significant decrease in fasting insulin, as compared to control participants. The effects of exercise and metformin on metabolic markers were suggestive of an additive effect, as compared to the effect of either intervention alone, though power limited demonstration of additivity or synergy.

Table 1. Baseline characteristics*

All	Metformin + exercise (N = 35)	Exercise only (N = 35)	Metformin only (N = 35)	Control (N = 34)
Tumor location, No. (%)				
Breast cancer	22 (62.9)	21 (60.0)	22 (62.9)	22 (64.7)
Colorectal cancer	13 (37.1)	14 (40.0)	13 (37.1)	12 (35.3)
Female, No. (%)	29 (82.9)	29 (82.9)	29 (82.9)	29 (85.3)
Study site, No. (%)				
Dana-Farber	28 (80.0)	22 (62.9)	24 (68.6)	25 (73.5)
Duke	4 (11.4)	4 (11.4)	5 (14.3)	6 (17.6)
Yale	3 (8.6)	9 (25.7)	6 (17.1)	3 (8.8)
Age, median (IQR), y	53.4 (47.9–58.5)	58.4 (49.3–64.6)	54.7 (49.5–60.9)	56.1 (48.1–65.9)
Years from diagnosis to registration, median (IQR)	2.0 (1.1–3.8)	1.8 (1.0–4.8)	2.5 (1.3–4.9)	1.4 (1.0–2.8)
Cancer stage, No. (%)				
I	14 (40.0)	11 (31.4)	14 (40.0)	12 (35.3)
II	8 (22.9)	11 (31.4)	9 (25.7)	12 (35.3)
III	13 (37.1)	12 (34.3)	12 (34.3)	9 (26.5)
Unknown	0 (0.0)	1 (2.9)	0 (0.0)	1 (2.9)
Prior chemotherapy, No. (%)	25 (71.4)	22 (62.9)	23 (65.7)	22 (64.7)
Prior radiation, No. (%)	17 (48.6)	16 (45.7)	14 (40.0)	16 (47.1)
Weight, median (IQR), kg	78.1 (68.9–92.5)	82.2 (68.8–96.8)	81.1 (73.0–99.4)	75.3 (68.3–91.5)
BMI, median (IQR)	27.7 (25.5–34.2)	28.5 (26.4–32.8)	29.0 (26.4–36.2)	28.4 (25.5–31.9)
Waist-to-hip ratio, median (IQR)	0.82 (0.76–0.90)	0.84 (0.78–0.91)	0.84 (0.78–0.91)	0.85 (0.80–0.91)
Waist, median (IQR), cm	94.5 (80.8–100.2)	94.6 (85.3–101.0)	97.5 (84.5–102.5)	90.6 (80.9–107.5)
Hip, median (IQR), cm	107.0 (101.0–120.2)	110.3 (103.8–118.0)	110.4 (100.3–120.0)	110.5 (100.5–118.0)
Exercise, minutes/week, median (IQR)	30 (0–87)	21 (0–90)	45 (0–70)	42 (0–100)
Physical activity, MET hours/week, median (IQboR)	2.0 (0.0–5.3)	1.2 (0.0–5.8)	3.4 (0.0–4.7)	2.7 (0.0–6.7)
Walking distance in 6 min, median(IQR), ft	1495 (1439–1745)	1572.0 (1410–1737)	1551 (1495–1736)	1556 (1476–1706)
Insulin, median (IQR), μU/L	8.2 (6.2–10.8)	8.2 (6.2–11.8)	10.8 (5.2–14.7)	7.5 (6.0–13.5)
Glucose, median (IQR), mg/dL	86.0 (80.3–93.4)	87.2 (82.0–97.9)	89.8 (80.8–104.5)	87.4 (79.2–100.8)
HOMA, median (IQR)	1.5 (1.3–2.3)	1.8 (1.3–2.8)	2.0 (1.1–3.7)	1.7 (1.1–3.1)
Leptin, median (IQR), ng/mL	21.8 (14.3-30.9)	24.1 (16.7–38.2)	25.7 (10.8–43.0)	30.3 (22.2–39.0)
IGF-I, median (IQR), ng/mL	100.9 (87.9–123.8)	111.4 (73.0–139.7)	104.1 (82.7–142.4)	88.7 (81.6–109.2)
IGFBP 3, median (IQR), ng/mL	4426 (3845–5148)	4282 (3521–4921)	4210 (3644–4874)	4250 (3846–4940)

*HOMA = homeostatic model assessment for insulin resistance; IGF = insulin-like growth factor; IGFBP = insulin-like growth factor binding protein; IQR = intraquartile range; MET = metabolic equivalent task; ng = nanograms; μU = microunits.

Table 2. Change in exercise behaviors and fitness by treatment arm

Measurement	Metformin + exercise (arm 1) absolute change, minutes (SE)	*P* arm 1 vs 4*	Exercise only (arm 2) absolute change (SE)	*P* arm 2 vs 4*	Metformin only (arm 3) absolute change (SE)	*P* arm 3 vs 4*	Control (arm 4) absolute change (SE)	*P* arm 1 vs 2†	*P* arm 1 vs 3†
Exercise, min/wk	166.6 (16.4)	< .0001	140.3 (16.4)	< .0001	26.9 (17.7)	0.69	30.2 (19.4)	.07	< .0001
Physical activity, MET h/wk	13.6 (1.26)	< .0001	11.3 (1.26)	< .0001	2.40 (1.36)	0.65	2.76 (1.49)	.04	< .0001
Walking distance in 6 min, ft	105.4 (23.6)	.02	81.9 (24.5)	.09	−2.02 (26.1)	0.92	39.9 (28.2)	.20	< .0001

*One-sided *P* tests if the decrease in treatment arms is greater than in the control arm. Analyses by mixed modeling. MET = metabolic equivalent task.
†One-sided *P* tests if the decrease in the combined arm is greater than in the exercise-only arm or metformin-only arm.

A number of studies, primarily in breast cancer, have demonstrated the effects of exercise or metformin on metabolic markers (26,27,29,42–45,52). Recent meta-analyses reported statistically significant reductions of fasting insulin and non–statistically significant reductions in insulin resistance, adiponectin, and C-reactive protein (CRP) with exercise (53) and statistically significant reductions in fasting insulin and glucose, CRP, HOMA, BMI, and leptin with metformin (54) in breast cancer patients. The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MA.32 trial demonstrated that 6 months of metformin led to an 11.1% decrease in insulin ($P = .002$) and a 3% decrease in weight ($P < .001$) relative to controls (52).

There are a few studies that have looked at the effect of combining or comparing the effects of different types of interventions that target metabolic markers in cancer populations. One recent report by Patterson et al investigated the impact of metformin or a weight loss intervention, alone or in combination, on metabolic, inflammatory and sex steroid biomarkers in 333 postmenopausal breast cancer survivors with BMI greater than

Table 3. Compliance* with assigned treatments

% completed	Exercise in combined arm N = 35	Exercise in exercise only N = 35	Metformin in combined arm N = 35	Metformin in metformin only N = 35
90–100	5 (14.3)	7 (20.0)	14 (41.2)	10 (28.6)
75–89	15 (42.9)	10 (28.6)	7 (20.0)	8 (22.9)
50–74	8 (22.9)	9 (25.7)	6 (17.1)	2 (5.7)
10–49	2 (5.7)	5 (14.3)	2 (5.7)	6 (17.1)
0–9, missing	5 (14.3)	4 (11.4)	6 (17.1)	9 (25.7)

*Compliance rate: required exercise sessions 24; required metformin intake is based on drug log, or 154 pills if no records.

Table 4. Toxicity for metformin, highest grade for each patient

Toxicity	Metformin + exercise, No. (%)				Metformin only, No. (%)			
	Any grade	Grade 1	Grade 2	Grade 3	Any grade	Grade 1	Grade 2	Grade 3
Diarrhea	14 (40)	8 (22.9)	2 (5.7)	2 (5.7)	8 (22.9)	6 (17.1)	1 (2.9)	1 (2.9)
Nausea	5 (14.3)	4 (11.4)	0	1 (2.9)	9 (25.7)	6 (17.1)	3 (8.6)	0
Abdominal Pain	6 (17.1)	5 (14.3)	1 (2.9)	0	6 (17.1)	4 (11.4)	1 (2.9)	1 (2.9)
Vomiting	3 (8.6)	2 (5.7)	0	1 (2.9)	7 (20.0)	3 (8.6)	4 (11.4)	0
Bloating	3 (8.6)	1 (2.9)	2 (5.7)	0	3 (8.6)	1 (2.9)	2 (5.7)	0
Flatulence	4 (11.4)	3 (8.6)	1 (2.9)	0	2 (5.7)	1 (2.9)	1 (2.9)	0
Fatigue	2 (5.8)	1 (2.9)	1 (2.9)	0	2 (5.7)	1 (2.9)	1 (2.9)	0

Table 5. Effect of exercise and metformin on biomarkers and anthropometric measures (difference in least square means and standard error)

Measurement	Metformin + exercise (arm 1) absolute change (SE) (% change [SE])	P arm 1 vs 4*	Exercise only (arm 2) absolute change (SE) (% change [SE])	P arm 2 vs 4*	Metformin only (arm 3) absolute change (SE) (% change [SE])	P arm 3 vs 4*	Control (arm 4) absolute change (SE) (% change [SE])	P arm 2 vs 1†	P arm 3 vs 1†
Blood markers changes									
No.	33		34		32		29		
Fasting insulin, μU/L	−2.47 (1.07)	< .0001‡	−0.08 (1.06)	.01‡	−1.16 (1.18)	.003‡	2.79 (1.27)	.03‡	.11
	−32.3% (3.2)		−1.2% (0.2)		−12.9% (1.9)		32.7% (4.7)		
Glucose, mg/dL	−0.09 (2.11)	.007‡	2.93 (2.08)	.17	−4.11 (2.32)	.0004‡	4.92 (2.44)	.04	.88
	−0.1% (0)		3.3 % (0.1)		−4.6% (0.2)		5.4% (0.3)		
HOMA IR	−0.50 (0.38)	.0002	0.01 (0.38)	.007‡	−0.41 (0.42)	.0009 ‡	1.16 (0.45)	.09	.38
	−30.6% (3.0)		0.4 % (1.0)		−22.1% (3.8)		61.2% (11)		
Leptin, ng/mL	−5.09 (1.21)	.0002‡	−0.54 (1.19)	.33	−2.56 (1.33)	.07	−0.20 (1.40)	.0002‡	.02‡
	−42.2% (11.7)		−4.0 (1.0)		−15.2 (3.5)		−0.8% (0.1)		
IGF 1 ng/mL	−1.29 (2.98)	0.72	8.22 (2.94)	1.00	−2.66 (3.28)	.63	−3.05 (3.46)	.0008‡	.59
	−1.2% (0.1)		8.9% (0.6)		−2.4% (0.2)		−3.1% (0.2)		
IGFBP 3, ng/mL	−178.8 (82.0)	.75	53.4 (80.7)	.05	25.9 (90.2)	.11	−96.9 (94.9)	.99	.98
	−4.3% (0.2)		1.4% (0.11)		0.61% (0.03)		−2.3% (0.12)		
Anthropometric changes									
Weight, kg	−1.37 (0.30)	< .0001	−0.17 (0.31)	< .0001	−0.81 (0.33)	< .0001	1.24 (0.35)	.0002	.05
	−1.8 % (0.1)		−0.22% (0.01)		−1.0% (0.1)		1.55% (0.1)		
BMI, kg/m^2	−0.50 (0.11)	< .0001	−0.07 (0.11)	< .0001	−0.29 (0.12)	< .0001	0.43 (0.12)	.0001	.05
	−1.74% (0.1)		−0.24% (0.01)		−1.0% (0.1)		1.43% (0.1)		
Waist-to-hip ratio	−0.007 (0.01)	.01	0.006 (0.01)	.21	0.012 (0.01)	.38	0.016 (0.01)	.06	.02
	−0.78% (0.02)		0.74% (0.02)		1.45% (0.03)		1.91% (0.04)		
Waist, cm	−1.31 (0.90)	.0004	−1.51 (0.91)	.0005	1.32 (0.98)	.22	2.40 (1.04)	.51	.004
	−1.42% (0.1)		−1.60% (0.04)		1.44% (0.1)		2.53% (0.1)		

*One-sided *P* tests if the decrease in treatment arms is greater than in the control arm. Mixed model adjusted for baseline biomarker or anthropometric value, BMI (30 or greater or not), sex (female, male), cancer (breast or colorectal), study site. BMI = body mass index; HOMA IR = homeostatic model assessment for insulin resistance; IGF-1 = insulin-like growth factor–1; IGFBP-3 = insulin-like growth factor binding protein–3 Negative least square means indicate a decrease at 3 months compared to baseline value.

†One-sided *P* tests if the decrease in the combined arm is greater than in the exercise-only arm or metformin-only arm.

‡Indicates statistically significant differences based on Holm's method.

25 kg/m^2 (55). Weight loss and metformin both led to reductions in fasting insulin as compared to controls. Reduction in insulin was numerically greater in patients who received both interventions than either intervention alone. Notably, metformin led to a median 5.3% weight loss, compared to 5.5% in the weight loss groups (and 2.7% in the control group), making it more challenging to separate the effects of the drug vs weight loss. The CHOICE Study assigned 370 breast cancer survivors with a BMI of 25–35 kg/m^2 to a calorie-restricted low-carbohydrate diet, a calorie-restricted low-fat diet, or to a usual diet control (56). The study demonstrated statistically significant reductions in fasting glucose and other metabolic markers in both diet groups and found the magnitude of change was directly dependent on amount of weight lost.

Such comparative studies will be essential in determining which types of energy-balance interventions may be the most effective in subgroups of patients defined by cancer types and host characteristics. Cancer treatments have become increasingly specialized, focusing on individual targets within cancer cells and genetic factors. Observational evidence increasingly shows associations between host factors—physical activity, dietary elements, adiposity, and use of drugs like metformin—and cancer outcomes, but these types of data make it difficult to determine which types of interventions will benefit which patients. Randomized trials that compare the effects of different energy-balance interventions, alone and in combination, on biomarkers linked to cancer recurrence and mortality will not only provide mechanistic insight into the biological pathways through which energy-balance factors affect cancer outcomes, but also demonstrate the most effective means to use energy-balance strategies to improve prognosis in cancer patients.

A number of limitations of our trial must be acknowledged. Our study was slow to accrue participants, especially those with colorectal cancer, ultimately preventing us from meeting our target enrollment goal and limiting power for many of our analyses. Other studies have demonstrated slow accrual of colorectal cancer patients to energy-balance intervention studies. The reasons for this are not entirely clear but may be related to degree of symptom burden after completion of systemic therapy in this population. We also had a higher-than-anticipated rate of attrition, with 35% of participants not completing the 12-week intervention and follow-up period. Adherence to the exercise intervention was good, with exercise participants increasing weekly minutes of moderate or vigorous activity by 140–167 minutes/week, vs 30 minutes in controls ($P < .001$). Adherence to the metformin intervention was more problematic, with only 51% of patients taking at least 75% of prescribed doses. The dosage was similar to that used in other cancer studies, including NCIC CTG MA.32 in breast cancer (43) and a study in advanced pancreatic cancer with standard chemotherapy (which dosed up to 1000 mg twice a day) (57). Notably, Patterson et al also reported moderate rates of noncompliance with metformin, with only 65.9% of participants taking greater than 80% of prescribed pills (55). These compliance rates are lower than have been reported in the diabetes literature (58) and may reflect the relative inexperience of oncologists in managing the gastrointestinal toxicity of metformin or differences in the patient populations including motivation to continue treatment. It is possible that larger differences in biomarkers would have been seen with better adherence to metformin.

In conclusion, in one of the first trials evaluating the effects of two different energy-balance interventions, independently and in combination, on metabolic biomarkers in breast and colorectal cancer survivors, our study demonstrates that both exercise and metformin statistically significantly lowered levels of fasting insulin and led to improvements in other metabolic biomarkers. Changes from combination of the two interventions suggested larger reduction in biomarkers than either intervention alone, despite modest compliance to the prescribed metformin dosage. These findings require validation in future studies, with efforts to improve compliance particularly for metformin, but they could help inform future management of patients after cancer diagnosis.

Funding

This work was supported by the Transdisciplinary Research on Energetics and Cancer mechanism from the National Cancer Institute; grant funding U54 CA155626. LWJ is supported by AKTIV Against Cancer, The KavliTrust, and the Memorial Sloan Kettering Cancer Center Support Grant/Core Grant (P30 CA008748). JAM is supported by the Douglas Gray Woodruff Chair Fund, the Guo Shu Shi Fund, Anonymous Family Fund for Innovations in Colorectal Cancer, and the George Stone Family Foundation. JAL is supported by the Susan G. Komen Foundation.

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JAM received institutional research funding from Boston Biomedical and Biothera, and has served as an advisor/consultant to Ignyta and Cota. SMT receives institutional research funding from Novartis, Genentech, Eli Lilly, Pfizer, Merck, Exelixis, Eisai, Bristol-Myers Squibb, AstraZeneca, Cyclacel, Immunomedics, Odenate, and Nektar; and has served as an advisor/consultant to Novartis, Eli Lilly, Pfizer, Merck, AstraZeneca, Eisai, Puma, Genentech, Immunomedics, Nektar, Tesaro, and Nanostring. C.S.F. holds ownership interest (including patents) in Cytomx Therapeutics andEntrinsic Health, and is an advisory board member/unpaid consultant forAgios, Bain Capital, Bayer, Celgene, Dicerna, Five Prime Therapeutics, GileadSciences, Eli Lilly, Entrinsic Health, Genentech, KEW, Merck, MerrimackPharma, Pfizer, Sanofi, Taiho, Unum Therapeutics, and CytomX Therapeutics. K.N. is an employee/paid consultant forSeattle Genetics, Bayer, Lilly, Genentech, and Tarrex, and reports receivingcommercial research grants from Pharmavite, LLC, Genentech, Gilead,Tarrex, Trovagene, and Celgene. The funders had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

ClinicalTrials.gov Identifier: NCT01340300.

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