Effect of a tailored technology-enhanced home-based exercise program on DNA methylation change among cancer survivors with multiple chronic conditions

Summary of project aims

More than 16.9 million cancer survivors live in the United States, and that number will increase to more than 22.1 million by 2030 (Miller et al., 2019). Over 80% of these cancer survivors have one or more chronic conditions, including type 2 diabetes, cardiovascular diseases, and osteoarthritis (Rothrock et al., 2010). Cancer survivors with multiple chronic conditions (MCCs) experience significantly higher symptom prevalence and severity (e.g., pain, fatigue) than those without any comorbidities (Annunziata et al., 2013; Arrieta et al., 2013; Han et al., 2020; Huang et al., 2017; Manning & Bettencourt, 2011). These multiple symptoms are negatively associated with the health-related quality of life and adherence to treatment (Schmidt et al., 2015; Shelby et al., 2011). Managing MCCs is often challenging due to the complexity of conditions and symptoms.

Physical activity (PA) is one of the non-pharmacological and cost-effective strategies that showed beneficial effects on improving physical and psychological symptoms, physical functioning, resilience, and overall quality of life among patients with chronic illnesses (Alfano et al., 2007; Ferioli et al., 2018; Lin, Y. et al., 2015; Sylvester et al., 2017). The recommendations for PA in cancer survivors is at least 150 min of moderate-intensity PA per week (Rock et al., 2012). Moderate-intensity physical activity is defined as 3.0–6.0 exercise metabolic rates (METs) (World Health Organization, 2010). However, more than 50% of cancer survivors fail to satisfy these guidelines (Underwood et al., 2012). To overcome barriers to exercise, home-based exercise programs have been developed. Reports have shown promising effectiveness on pain, fatigue, and quality of life among persons with several chronic

conditions (Dodd et al., 2010; Hoffman et al., 2013; Kim et al., 2019). Recent evidence shows that using technology to provide immediate feedback on physical performance, reminder messaging, and internet or application-based telehealth programs can increase PA motivation and adherence (Evans et al., 2021; Lambert et al., 2021; Timmerman et al., 2017). Studies have reported promising effectiveness of a home-based exercise intervention on self-reported symptoms and quality of life among patients with cancer and other chronic illnesses (Kim et al., 2019; Kokts-Porietis et al., 2019; Loh et al., 2019; Nyrop et al., 2018; Stefani et al., 2019; Wang et al., 2019). However, the effect of home-based exercise on biological and physiological outcomes are inconsistent.

Biological age is also known as physiological age or phenotypic age. This concept represents the biological status of individuals. Telomere length has been a proposed method of determining biologic age in individuals. Telomeres are end cap proteins found on the end of eukaryotic chromosomes that serve to protect and maintain DNA integrity (Blackburn, 2001). Shortening telomeres renders inadequate telomere supply for the cell to further divide, leading to cell senescence. As a result of cell senescence, telomere length has been associated with several age-related diseases, including cancer (Fani et al., 2020; Jin et al., 2018; Xu et al., 2019; Zhang et al., 2017). Current data indicates that individuals with higher levels of physical activity and individuals engaging in aerobic exercise, resistance, and yoga exhibit a longer telomere length (Arsenis et al., 2017; Lin, X. et al., 2019). However, the overall relationship between telomere length and physical activity was weak, and the results varied depending on the participants. DNA methylation age is a newer method being used to determine biologic age.

DNA methylation (DNAm) age, one of the epigenetic age estimators, predicts biological age by measuring the change of methylated patterns in DNA (Horvath & Raj, 2018). The DNAm age is the most promising biological age estimator compared to telomere length,

transcriptomic-based estimators, and proteomic-based estimators (Jylhävä et al., 2017). Epigenetic modification can be caused by nutrition, stress, physical activity, smoking, and alcohol consumption, the so-called "environmental exposure or lifestyle." Thus, this epigenetic estimator may have a crucial role as a biomarker of complex symptoms and disease. Studies found that DNAm age acceleration was associated with mortality, cancer, frailty, sleep, Alzheimer's disease, and cognitive impairment (Breitling et al., 2016; Carroll et al., 2017; Dugué et al., 2018; Levine et al., 2015; Levine et al., 2018; Lu et al., 2017; Marioni et al., 2015; Perna et al., 2016). Recent studies suggest significant associations among physical activity, cognitive performance, pain, anxiety, and DNAm age among older adults (Kwiatkowska et al., 2020; Maddock et al., 2020; Marečková et al., 2020). Several studies have reported the effects of an aerobic exercise program on DNA methylation in cancer survivors (Ferioli et al., 2018; Gillman et al., 2018; Hunter et al., 2019). However, it is unclear whether home-based exercise will have the same effect on DNAm age; especially among the cancer survivors with MCCs. The DNAm is a novel measure of intervention impact in nursing. It may be a more sensitive measure to assess intervention effectiveness rather than a self-report questionnaire (McBride & Koehly, 2017). DNAm may improve our understanding of the underlying mechanisms of nursing interventions such as home-based exercises and may serve as a biomarker to advance precision health in nursing research.

This study aims to (1) examine the pre-and-post tailored home-based exercise (iHBE) program epigenetic changes (2) examine the associations of changes in DNAm age with symptoms (pain, fatigue, cognitive function) and resilience at completion (12-week) compared to baseline data collected from cancer survivors living with MCCs.

Theoretical/conceptual framework

To better understand the associations of epigenetic changes related to an iHBE program, we will use the "University of Illinois at Chicago (UIC) model for genetic and epigenetic research" which is developed as a theoretical framework to guide nursing genetic research (Maki & DeVon, 2018). In 2018, this UIC model developed based on the Martha Rogers' theory of unitary human beings show a contemporary view of how to interact genetic (innate) and epigenetic mechanism to phenotype by regulating transcription or translation processes. In this study, we will investigate the epigenetic changes related to the iHBE program among cancer survivors living with one or more comorbid chronic conditions. The iHBE program-related epigenetic changes may explain improvement in physical activity, well-being, and resilience as a phenotype. The results will provide a better understanding of the mechanism of action of iHBE effects by comparing DNAm patterns between baseline and post-intervention changes. These findings will help future development of effective self-management programs.

Methods

Participants

This study is a sub-study of a pilot randomized clinical trial (NCT03874754) exploring the feasibility and effect of iHBE program on symptoms, resilience, and affective well-being of cancer survivors with MCCs. Cancer patients who were diagnosed with at least one comorbidity were recruited into the study. The parent study's inclusion criteria were (1) participants diagnosed with solid tumor cancer who have completed cancer treatment and diagnosed with diabetes and/or hypertension for at least a year; (2) aged 21 years or older. Exclusion criteria were those (1) currently undergoing cancer treatment; (2) have an active infection; and (3) diagnosed with a psychological disorder. For this sub-study, participants who complete the 12 weeks program with completed questionnaire data and have at least 1 blood

samples were included. Study outcomes were collected at baseline and at completion of the program (12 weeks).

Intervention

The iHBE Program was a 12-week program with two home visit assessment session (before and after 12 weeks program), two home visits during exercise, and nine follow-up phone calls. The exercise intervention will be tailored based on (1) participants' goals and preference (participants can choose to exercise using The NIA Go4Life exercise or Iyengar-style yoga 10-20 minutes on at least two days per week or walking to achieve a weekly goal (e.g., walk 5 min for three days/week and increase 1-2 min/week);or Modified Otago exercise intervention (2) participants' physical conditions The technologies, a wearable device (FitBit), and amobile ecological momentary application (mEMA), were used to monitor physical activity (heart rate, step count) and daily symptoms. The data from wearable device and mEMA was used to provide weekly performance report and feedback.

Randomization

The participants in the parent study were randomly assigned to the experimental (exercise) or control groups using the Microsoft excel randomization table based on their gender (male and female) and age (< 65 and ≥ 65 years old).

Measurements

The pain was measured by PROMIS Pain Intensity – Short Form 3a V1.0. It is a universal

instrument for pain, consisting of 3-items (worst, average, and current pain) measure from 1 (no pain) to 5 (very severe). PROMIS Pain Intensity has been reported conceptually validated with established reliability test-retest values = .83 to .93 (Broderick et al., 2013). PROMIS Short Form V1.0-Fatigue 6a evaluated the level of fatigue to assess the fatigue level. It consists of 6 items and self-reported fatigue (frequency, duration, intensity) and the impact on physical, mental, and social activities, has five response options (1 or never to 5 or always). The reliability of the instrument (Cronbach's α) was 0.93 (Pokrzywinski et al., 2020). Cognitive function was measured by the Multiple Ability Self-Report Questionnaire (MASQ) and Montreal Cognitive Assessment (MoCA). The MASQ was developed to assess the self-perception of cognitive difficulties. It is 38 items about perceived cognitive difficulties in 5 domains (language, visual perceptual ability, verbal memory, visual-spatial memory, and attention/concentration) self-report rating scale of 1 (Never) to 5 (Always). Cronbach's alpha of MASQ was 0.92 (Seidenberg et al., 1994). The MoCA was developed to evaluate cognitive domains, including short-term memory recall task, attention, executive functions, and visuospatial abilities, etc. Cronbach's alpha in cancer survivors was 0.79 (Wazqar, 2019). Connor-Davidson Resilience Scale (CDRS) was used to measure the resilience of participants. It is a 10 item self-report rating scale of 0 (not true at all) to 4 (true nearly all the time). Cronbach's alpha of CDRS was 0.83 (Campbell-Sills & Stein, 2007).

Step counts

Fitbit Charge 3 devices were placed on participants' nondominant wrists during 12-week intervention. Participants were instructed to always wear the device, except during charging. We extracted a daily step and analyzed by averaging the daily step count per week.

Data collection

Participants completed the questionnaires for symptoms, well-being, and resilience at baseline and after completing the 12-week program. The participant's blood was collected in an EDTA tube and was stored in a -80°C freezer. Genomic DNA extraction and methyl array were done by outsourcing the Zymo Research.

DNA methylation age calculation

DNA methylation age calculation was performed using DNAge® analysis at Zymo Research (Irvine, California, USA). DNA was extracted from human blood cells by Quick-DNA™ Miniprep Plus kit (Zymo Research, Irvine, California, USA). Bisulfite conversion was performed to deaminate cytosine into uracil using the EZ DNA Methylation-Lightning™ Kit (Zymo Research, Irvine, California, USA) according to the manufacturer's guidelines. Bisulfited DNA was enriched for sequencing of >500 DNA methylation age-associated gene loci. DNA methylation values were obtained from the sequence data and used to assess DNA age according to Zymo Research's proprietary DNAge® predictor.

Analysis

All analyses were conducted using SPSS version 25.0 (IBM SPSS Statistics, SPSS, Chicago, IL, USA). The p-value of ≤ 0.05 was considered statistically significant. Data were denoted as mean ± standard deviation, and categorical variables were expressed in numbers.

Summary of findings

Demographic characteristics of participants

Four participants were randomly assigned in the exercise group and four in the control group. Eight participants age range from 63 to 80 (mean ± SD = 74.8 ± 6.6) who meet the inclusion and exclusion criteria for this sub-study was included in the sub-study. Two subjects were males, and six were female. Two participants identified as white, and the remaining six subjects identified as Black or African American. Four participants indicated less than college, three reported having graduated from college, and the remaining one had graduate degree. Six participants reported being retired, one was still working, and one was disabled, permanently or temporarily. Five participants indicated they were divorced, while one indicated that they have never been married and one were still married. Within the last 12 months, three participants were diagnosed with hypertension, two were diagnosed with type 2 diabetes, and three participants was diagnosed with both comorbidities. Three participants had multiple cancer sites and five participants indicated one cancer site (Table 1).

DNA methylation Age, Outcomes Changes Before and After the Program

Due to the impact of COVID-19 pandemic on the parent study, the data collection was interrupted. Among these 8 participants, there were only 4 participants who we were able to complete the blood sample collection for the epigenetic changes with only 1 participant in the exercise group. The DNA methylation age result showed that although the biological age was less than chronological age, the participant in the exercise group had increase biological age acceleration (0.5 year increase) with highest change of step counts at the 12 weeks compare to baseline (78% increase in step count from baseline). This participant reported biggest

improvement of symptoms (19% reduction of pain, 9% reduction of fatigue, 65% reduction of insomnia, 9% improve of MoCA, and average of 36% improve 5 domains of cognitive function in MASQ) and 8% improvement of resilience) (Table 2).

Association among DNA methylation Age, Symptoms and Resilience

Table 3 shows the associations between DNA methylation age and symptoms. The DNA methylation age was significantly correlated with MoCA score (r = .563, p = .028). Other symptoms and resilience were not shown significant correlation with DNA methylation age. Table 3 shows the associations between DNA methylation age, symptoms, and resilience. The DNA methylation age was significantly correlated with MoCA (r = .563, p = .028). The DNA methylation did not show other symptoms and resilience significantly correlated with DNA methylation age. The pain was positively associated with fatigue (r = .687, p = .007) and insomnia was correlated with the verbal memory domain of MASQ (r = .788, p < .001). The resilience was negatively associated with the fatigue (r = -.518, p = .042). The resilience was also correlated with the language (r = -.642, p = .012), verbal memory (r = -.600, p = .020), visual spatial memory (r = -.868, p < .001), and attention (r = -.534, p = .037), domain of MASQ.

Recommendations

Due to the COVID-19 situation, we have faced the difficulty of data collection in the parent study; we analyzed only one participant of the intervention group. Although it is hard to compare the effect of DNA methylation age change to pre-and post-intervention, in this study, we found that the DNA methylation age is positively associated with cognitive function. We

recommend repeated research using larger sample sizes.

Research Grant Financial Summary

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Principle Investigator (s):

1. Jongmin Park

College of Nursing, Pusan National University, Gyeongsangnam-do 50612, Republic Korea

email: jmpark@pusan.ac.kr

2. Nada Lukkahatai

Johns Hopkins School of Nursing, 525 North Wolfe Street, Baltimore, MD 21205

e-mail: nada.lukkahatai@jhu.edu

Financial Report

Categories	Amount Requested	Actual Expenses
Personnel *(Requests for Principal Investigator salary only may be included. Include hourly rate for PI in justification section.)*	0	0
Secretarial staff	0	0
Typing Costs *(must be those directly related to the research. Typing of dissertations will not be funded.)*	0	0
Research Assistants	0	0
Consultants *(Limit to $50 per hour)*	0	0
Supplies	5000	
- Supplies and reagent for DNA isolation		200
- Supplies and reagent for Infinium Human Methylation EPIC array		4,800
Computer Costs *(software only)*	0	0
Travel Expenses *(data collection only)*	0	0
Other	0	0
Total Amount:	5000	5000

Table 1. Demographics and general characteristics of participants

Participants	Age	Gender	Race	Ethnicity	Education	Employment	Marital status	Chronic illness	Cancer site(s)
A	77.0	Male	Black or African American	Not Hispanic or Latino	College graduate	Retired	Never married	Type 2 diabetes	Prostate, Lung
B	79.0	Male	White	Not Hispanic or Latino	Less than college	Working now	Divorced	Both	Bladder, Melanoma
C	75.0	Female	White	Not Hispanic or Latino	College graduate	Retired	Divorced	Type 2 diabetes	Endometrial
D	78.0	Female	Black or African American	Hispanic or Latino	Less than college	Retired	Divorced	Hypertension	Breast
E	80.0	Female	Black or African American	Not Hispanic or Latino	Less than college	Retired	Divorced	Both	Ovarian
F	63.0	Female	Black or African American	Not Hispanic or Latino	College graduate	Disabled, permanently or temporarily	Widowed	Hypertension	Uterus
G	80.0	Female	Black or African American	Not Hispanic or Latino	Less than college	Retired	Divorced	Both	Breast, Uterus
H	66.0	Female	Black or African American	Not Hispanic or Latino	Graduate degree	Retired	Widowed	Hypertension	Ovarian

Table 2. DNA methylation age, symptoms, and resilience changes between pre- and post-intervention

Participants	Group	Age	Pre-DNAm age	Post-DNAm age	Δ DNAm age	%change of symptoms			%change of cognitive function						% change of resilience	%change of average step count
										MASQ						
						Pain	Fatigue	Insomnia	MoCA	Language	Visual perceptual ability	Verbal memory	Visual spatial memory	Attention		
A	Control	77.0	73.7	75.1	1.4	0.0	0.0	-50.0	0.0	18.2	5.6	5.6	23.1	7.7	0.0	-25.6
B	Control	79.0	75.9	75.7	-0.2	6.6	3.3	25.0	-3.4	18.2	0.0	5.3	-9.1	-5.6	6.8	53.22
C	Control	75.0	75.1	75.6	0.5	23.2	-6.1	4.8	7.7	7.7	0.0	8.0	0.0	12.5	2.6	-44.50
D	Intervention	78.0	75.0	75.5	0.5	-18.8	-9.4	-65.4	9.1	-33.3	-26.7	-62.5	-15.0	-45.0	8.1	78.28
E	Intervention	80.0	N/A	84.0	N/A	-13.3	-4.1	18.8	-10.7	25.0	-5.6	21.1	0.0	14.3	-7.3	28.88
F	Intervention	63.0	N/A	68.6	N/A	16.9	-8.7	-22.7	-21.4	0.0	16.7	133.3	-7.1	-30.8	-8.7	-26.16
G	Control	80.0	N/A	72.9	N/A	23.2	60.8	-25.0	11.8	8.7	-14.3	-4.5	16.7	-21.7	-5.1	NA
H	Intervention	66.0	66.1	N/A	N/A	-23.6	-3.6	-22.2	NA	-16.7	0.0	18.8	7.7	5.9	0.0	-14.08

Note. DNAm, DNA methylation; N/A, not available; MoCA, Montreal Cognitive Assessment; MASQ, Multiple Ability Self-Report Questionnaire

Table 3. Association among DNA Methylation Age, Symptoms and Resilience

Variables	1	2	3	4	5	6	7	8	9	10	11
1. DNA methylation age	1.000	-0.294	-0.423	0.243	.563*	0.021	0.089	0.230	-0.012	0.382	0.154
2. Pain		1.000	.690**	0.543	-0.123	0.052	-0.381	0.344	0.215	0.143	-.518*
3. Fatigue			1.000	0.351	-0.152	0.058	-0.425	0.436	0.094	0.036	-0.461
4. Insomnia				1.000	0.334	0.118	-0.272	.788**	0.185	0.433	-0.389
5. MoCA					1.000	-0.101	-.592*	0.043	-0.441	0.243	0.253
6. Language						1.000	0.392	0.369	.705**	.748**	-.642*
7. Visual perceptual ability							1.000	0.052	.576*	0.186	-0.167
8. Verbal memory								1.000	.548*	.499*	-.600*
9. Visual spatial memory									1.000	0.485	-.868**
10. Attention										1.000	-.534*
11. Resilience											1.000

Note. MoCA, Montreal Cognitive Assessment

*, $p < .05$; **, $p < .01$

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