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ORIGINAL CONTRIBUTION

Relationship between fruit and vegetable intake and interference control in breast cancer survivors

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Abstract
Purpose Nutrition plays an important role in brain structure and function, and the effects of diet may even be greater in those at greater risk of cognitive decline, such as individuals with cancer-related cognitive impairment. However, the relation of dietary components to cognitive function in cancer survivors is unknown. The objective of this study was to determine whether breast cancer survivors (BCS) evidenced impairments in interference control, a component of cognitive control, compared to age-matched women with no prior history of cancer, and to examine the moderating role of diet on cognitive function.
Methods In this cross-sectional study, a modified flanker task was used to assess interference control in BCS ($n = 31$) and age-matched women with no prior history of cancer ($n = 30$). Diet was assessed with 3-day food records. Differences between BCS and age-matched controls were assessed using linear mixed models, and multilevel regression analyses were conducted to assess the moderating role of diet on cognitive performance.
Results Cognitive performance was not different between groups. Fruit intake and vegetable intake were significantly associated with better performance on the incompatible condition of the flanker task (i.e., shorter reaction time and increased accuracy), independent of disease status. The association between dietary components and cognition was stronger for the incompatible incongruent condition, suggesting that fruit and vegetables may be important for the up-regulation of cognitive control when faced with higher cognitive demands.
Conclusions There was no difference in performance on an interference control task between BCS and age-matched controls. The data suggest that greater fruit intake and vegetable intake were positively associated with interference control in both BCS and age-matched controls.

Keywords Cognition · Fruit · Vegetable · Cancer survivors

Introduction

Breast cancer is the most common type of cancer in women in the USA and has a 5-year survival rate of 89 % [1]. As a result, there is a growing population of breast cancer patients and survivors that are living with treatment-related side effects, including cancer-related cognitive impairment [2]. Subjective cognitive dysfunction is a frequent complaint of breast cancer patients both during and after treatment [3], and typical concerns include memory lapses, difficulty concentrating, and slower processing speed [4, 5]. The prevalence of cancer-related cognitive impairment is estimated to range from 16 to 78 % [6], and evidence suggests that cognitive impairment can persist in up to 35 % of breast cancer survivors (BCS) 10–20 years following completion of treatment [7]. Multiple cognitive domains are thought to be impaired in cancer-related cognitive

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impairment, including memory, learning, attention, concentration, and visual–spatial skills [8], and the most commonly identified cognitive deficits are suggestive of disruption of the frontal-subcortical network systems [7]. Several mechanisms that contribute to cancer-related cognitive impairment have been proposed, including neurotoxicity due to treatments, oxidative stress, immune dysregulation, and psychological factors such as anxiety and depression [2]. Despite the high prevalence of cognitive dysfunction in BCS, evidence is lacking on how the impact of cancer and cancer treatment on brain function may be reduced or moderated.

Cognitive control, also referred to as executive function, reflects the ability to adapt one's actions in accord with internal goals [9]. The prefrontal cortex is believed to be responsible, in part, for supporting the cognitive processes of cognitive control which include inhibition, working memory, and cognitive flexibility [10]. These processes, which are important for mental and physical health, quality of life, and vocational success, have been shown to be adversely influenced by emotional distress, lack of sleep, and physical inactivity [10]. There is a growing body of evidence suggesting an association between cognitive function and diet. Although there have been mixed results from trials investigating supplementation with single nutrients [11–13], accumulating evidence supports the hypothesis that a diet that provides a combination of nutrients and phytochemicals may be beneficial for cognitive function. A plasma profile high in vitamins C and E, B vitamins, and vitamin D was associated with greater total cerebral volume and global cognitive function in older adults [14], and higher intakes of B12, vitamin D, and omega-3 from food were associated with lower amyloid-β load, a biomarker of Alzheimer's disease [15]. Fruit and vegetable consumption has been positively associated with global cognitive function [16, 17] and verbal memory [18], and a recent systematic review of nine longitudinal studies concluded that vegetable intake was associated with a reduced risk of dementia or cognitive decline [19]. The Mediterranean diet pattern, which is high in fruit and vegetables, olive oil, and fish and low in animal fats, has consistently been associated with better cognitive function, lower rates of cognitive decline, and reduced risk of Alzheimer's disease [20]. Furthermore, a large, 6.5-year randomized control intervention with a Mediterranean diet improved cognition in older adults [21]. Studies have suggested that the cognitive health benefits of fruits and vegetables may be mediated through the active dietary constituents in these foods including micronutrients and phytochemicals that may function as antioxidants. Fruits and vegetables are also sources of B vitamins that function as cofactors for neurotransmitter synthesis [22], and there is evidence that flavonoids found in various fruits and vegetables are neuroprotective, enhance neuronal function, stimulate neurogenesis, and suppress neuroinflammation [23]. Nutrition has an important role in brain structure and function [22, 24], and the effects might be greater in those with cognitive impairment or at greater risk for cognitive decline, such as individuals with cancer-related cognitive impairment. However, the relation of diet to cognitive function in cancer survivors is unknown.

The present study had two objectives. The first was to determine whether BCS evidenced impairments in interference control, an important component of cognitive control that reflects the ability to inhibit irrelevant aspects of the environment and focus attention toward relevant aspects of the environment, compared to age-matched women with no prior history of cancer. Our second aim was to examine fruit intake and vegetable intake as potential moderators of cognitive function. We hypothesized that interference control would be impaired in BCS and that higher fruit or vegetable intake would be associated with better cognitive control.

Experimental methods

Subjects

BCS were primarily recruited via a local oncology clinic. Oncology clinic research staff assisted with recruitment by screening physician schedules and reviewing patients' electronic medical records to identify those who were within 36 months of completing their primary therapy for breast cancer (i.e., including chemotherapy, radiation therapy or both) and potentially eligible for the study. In addition, BCS and age-matched controls were recruited using print media (newspapers, flyers), Web sites, and listserv announcements. After expressing initial interest, women were contacted by phone and provided a full study description. Inclusion criteria included: female; aged 18–70 years; able to walk unaided; no history of stroke or transient ischemic attack; no history of surgery that involved removal of brain tissue, not currently pregnant; be English-speaking; and no current use of computer-based brain training games (e.g., Lumosity®, BrainHQ®). BCS had to have been diagnosed with breast cancer and completed primary treatment (either chemotherapy, radiotherapy or both) within the past 36 months, and healthy controls must have had no previous cancer diagnosis. Consenting participants were screened for final eligibility using the mini-mental state examination (ineligible if score <23). Participants were scheduled for testing after passing study eligibility screening criteria. Participants were recruited from September 2013 through March 2014. Of the 141 total contacts, 73 consented and were eligible for testing (38 cancer, 35 control). Eleven women withdrew after consenting and did not complete testing owing to schedule conflicts ($n = 2$), no longer interested ($n = 3$), or unable to contact ($n = 6$). Sixty-two women (30 control; 32 breast cancer) consented and completed testing. However, one participant (BCS) did not complete a food record and was dropped from analyses. Participants were remunerated for their participation. All study procedures and recruitment materials were approved by the University of Illinois Institutional Review Board. Written informed consent was obtained from all subjects.

Breast cancer medical history

Participants provided self-report information on breast cancer-specific diagnosis and treatment history.

Demographics

Self-reported medical history, marital status, age, race, ethnicity, occupation, income, and education were collected.

Body mass index (BMI)

Height and weight were measured using a Seca electronic scale and stadiometer (Model 763 1321139, Chino, CA). Participants were measured while wearing light clothing and without shoes. BMI was calculated using the standard formula of weight (kg)/[height (m)^2].

Dietary intake

Participants completed a 3-day food record (1 weekend day and 2 weekdays), which were entered in Food Processor® (ESHA Research, Salem, OR) for analysis. The food processor software includes the USDA Standard Reference nutrient database and the USDA MyPlate food group information. A registered dietitian reviewed records with participants and entered all food records. Nutrient intake was normalized within participants to average intake per 1000 kcal.

Interference control

Participants were tested on an individual basis in a private, quiet area which was kept free of distractions. Cognitive testing was administered in the morning hours using a laptop computer and a handheld response pad (model TR-1 × 4-CR; Current Designs Inc., Philadelphia, PA). A modified flanker task [25–27] was used to assess interference control. Stimuli were 3.0-cm-tall white arrows presented focally on a black background for 116 ms with variable inter-stimulus interval of 1100, 1300, and 1500 ms. Stimulus congruent trials consisted of the central target arrow being flanked by an array of arrows facing the same direction (e.g., <<<<< or >>>>>). Stimulus incongruent trials consist of the central target arrow being flanked by an array of arrows facing the opposite direction (e.g., <<><< or >><>>). Incongruent trials require greater cognitive control to suppress the interference presented by flanking stimuli. Participants first completed the response compatible condition (defined in terms of the side of the response matching the direction of the central target arrow) in which they were instructed to attend to the central target arrow and press a button using their left thumb when the target arrow faces to the left (e.g., ‘<’) and a button press using their right thumb when the target arrow faces to the right (e.g., ‘>’). Task difficulty was further manipulated by introducing the response-incompatible condition. In the response-incompatible condition, participants were instructed to attend to the central target arrow and press a button using their left thumb when the target arrow faces to the right (e.g., ‘>’) and a button press using their right thumb when the target arrow faces to the left (e.g., ‘<’). The incompatible condition was always completed after the compatible condition. One block of 100 trials was administered in both the compatible and incompatible conditions, and each block consisted of 50 congruent trials and 50 incongruent trials. For both conditions, participants completed 40 practice trials.

The flanker task also measures changes in speed and accuracy across the congruent and incongruent conditions through the calculation of interference scores. These interference scores require simple subtractions across task conditions to yield the difference in performance between congruent and incongruent trials [28]. Interference scores for compatible and incompatible response accuracy (congruent–incongruent) and reaction time (incongruent–congruent) were calculated, with higher interference scores reflective of poorer maintenance of cognitive control.

Statistical analysis

Demographics and medical history were described using frequency and descriptive statistics to characterize study participants. Frequency distributions for the measures were examined to check for missing information and out-of-range values. Variable distributions were inspected, and a 5 % winsorization technique was applied to preserve the rank order of out-of-range values in the distribution, while limiting the influence of these values.

Our initial analysis examined mean-level differences in cognitive performance between breast cancer survivors and age-matched controls using linear mixed effects models. Cohen's *d*, [29] a distribution-based effect size measure, was calculated between groups for each outcome variable. Effect sizes were interpreted using Cohen's criteria of

.20 as a small effect, .50 as a moderate effect, and .80 as a large effect. Bivariate correlations were initially used to examine potential relations between proposed moderators and flanker performance (data not shown). Only significantly correlated ($\alpha < 0.05$) predictor variables were used in subsequent multilevel analyses. Multilevel regression analyses were then conducted to assess the moderating role of fruit intake and vegetable intake on interference control. Demographic variables (age, education, and income) were entered as covariates. Predictor variables were grand-mean centered to allow for inference of average predictor effects [30]. Models were developed in a stepwise fashion [31, 32], and final trimmed models were developed by entering all significant predictors and their interactions to test overall prediction of outcome variables (exclusion $p > 0.1$). Effect sizes from these models can in turn be interpreted using Cohen's criteria of .02 as a small effect, .13 as a moderate effect, and .26 as a large effect [29]. All data analyses were conducted using IBM SPSS version 22 (IBM, 2013).

Results

Participant characteristics

Table 1 summarizes participant characteristics. The mean age in BCS was 56.2 years of age and healthy controls was 55.2 years of age. There were no significant group differences in age, education, proportion of whites, socioeconomic status, or BMI. Disease and treatment characteristics of BCS are presented in Table 1. Most BCS had early stage breast cancer (80.6 % at stage II or lower), and time since completion of last treatment ranged from 2 to 33 months ($M = 15.7$, SD = 10.3). All had undergone surgery, 76.7 % had received radiation therapy, 64.5 % had received chemotherapy, and 77 % were currently receiving hormonal therapy.

Dietary intake

Overall, nutrient and food group intake were similar between BCS and age-matched controls (Table 2). Mean intake of fruits and vegetables in both groups were below the recommendations from the 2010 USDA dietary guidelines for women older than 50 years of age (i.e., 1.5 cups fruit a day, 2 cups of vegetables/day) [33].

Table 1 Sample characteristics of breast cancer survivors and age-matched controls

	Cancer $n = 31$	Control $n = 30$	Sig.
Age (Mean, SD)	56.2 (8.1)	55.2 (10.6)	.677
Income (*n*, %)			
≥$45,000	26 (77.4)	23 (76.7)	1.0
Race (*n*, %)			1.0
White	28 (90.3)	28 (93.3)	
Education (*n*, %)			
≥4 year college degree	20 (65.5)	23 (76.7)	.402
BMI (Mean, SD)	27.9 (5.5)	28.0 (5.9)	.942
Stage (*n*, %)			
DCIS	5 (16.1)	–	–
Stage I	9 (29.0)	–	–
Stage II	11 (35.5)	–	–
Stage III	3 (9.7)	–	–
Unknown	3 (9.7)	–	–
Treatment (*n*, %)			
Surgery	31 (100.0)	–	–
Radiotherapy only	11 (35.5)	–	–
Chemotherapy only	7 (22.6)	–	–
Chemotherapy plus radiotherapy	13 (41.9)	–	–
Hormonal therapy	22 (71.0)	–	–
Time since treatment—months (Mean, SD)	15.7 (10.3)	–	–

Table 2 Average daily intake in breast cancer survivors and age-matched controls

	Control		Cancer		Sig.
	Mean	SD	Mean	SD	
Total energy (kcal/day)	1764.4	482.0	1814.8	369.4	.642
Carbohydrate (g/day)	209.6	69.6	226.6	62.3	.311
Protein (g/day)	77.4	22.0	82.3	20.0	.360
Fat (g/day)	66.1	25.3	65.7	17.4	.944
Saturated fat (g/day)	21.1	1.6	22.3	1.6	.602
Unsaturated fat (g/day)	38.1	13.1	36.2	9.3	.516
Omega 3 fatty acids (g/day)	1.3	0.8	1.6	0.8	.252
Trans fat (g/day)	0.8	0.5	0.8	0.5	.724
Total dietary fiber (g/day)	19.4	5.1	21.0	6.3	.324
Soluble fiber (g/day)	2.2	1.3	2.9	1.9	.103
Insoluble fiber (g/day)	6.3	2.3	6.5	3.4	.827
Fruit intake (cups/day)	1.1	0.7	1.3	0.8	.429
Vegetable intake (cups/day)	1.8	1.1	1.6	1.1	.331

Cognitive task performance

In general, BCS performed similarly to age-matched controls on all measures of the flanker task (Table 3). Across both groups, reaction time (RT) was longer and accuracy decreased between compatible and incompatible conditions indicating greater demands on interference control. The decreased response accuracy and longer RT for incongruent trials compared with congruent trials, and further delays in RT and decreases in accuracy in the incompatible condition

Table 3 Comparison of cognitive test scores for age-matched controls and breast cancer survivors

	Control		Breast cancer survivors		Sig.	Cohen's d
	Mean	SE	Mean	SE		
Flanker compatible						
Congruent RT	429.48	9.13	427.18	8.97	.858	−.05
Congruent accuracy[a]	96.74	0.68	96.47	0.67	.777	−.07
Incongruent RT	474.32	11.00	475.01	10.82	.965	.01
Incongruent accuracy	93.13	0.87	93.21	0.85	.947	.02
RT interference	44.89	5.99	47.83	5.89	.723	.09
Accuracy interference	3.62	0.68	3.26	0.57	.714	−.09
Flanker incompatible						
Congruent RT	456.93	14.21	461.90	13.98	.804	.06
Congruent accuracy	92.89	1.96	89.36	1.93	.204	−.33
Incongruent RT	487.95	15.01	484.68	14.76	.877	−.04
Incongruent accuracy	89.00	2.22	89.62	2.19	.842	.05
RT interference	31.03	6.86	22.78	6.74	.395	−.22
Accuracy interference	3.89	1.11	−0.27	1.10	.010	−.68

RT reaction time in milliseconds

[a] Accuracy presented as % correct

compared with the compatible condition indicate a larger demand on interference control and attention in the incongruent and incompatible conditions.

Multilevel models were examined for the incompatible RT and accuracy for the congruent and incongruent conditions, as these outcomes were significantly correlated with fruit intake and vegetable intake as identified by bivariate correlations. Separate multilevel regression analyses were conducted using the four dependent incompatible flanker variables (congruent RT/accuracy and incongruent RT/accuracy). The direct effects of each dietary variable (fruit and vegetable) predicting each of the cognitive variables were analyzed separately. These findings are summarized in Table 4.

Incompatible congruent RT and accuracy

A significant main effect of fruit indicated that, regardless of disease status, those with higher fruit intake had better accuracy and shorter RT on congruent trials Table 4. A significant main effect for vegetable suggested that higher vegetable intake resulted in shorter RT. Additionally, participants with more education had better accuracy and shorter RT in congruent trials.

Incompatible incongruent RT and accuracy

Significant main effects of fruit and vegetables indicated that regardless of disease status, those with higher fruit or vegetable intake had better accuracy and shorter RT on incongruent trials Table 4. Additionally, those with higher education had shorter RT, and older participants were less accurate and had longer RT.

Discussion

Our results suggest that on a measure of interference control, BCS within 36 months of primary treatment performed similarly to age-matched women without a history of breast cancer. Meta-analyses of chemotherapy effects on cognitive function in BCS have concluded that the magnitude of cognitive impairment is generally small and subtle [34–36]. Additionally, several studies have reported hyperactivation and hyperconnectivity in frontal and parietal brain regions of BCS during cognitive tasks, potentially providing evidence of compensatory mechanisms that help BCS preserve cognitive performance and mask impairments [37–40]. Thus, imaging studies may provide additional information about the relationship between cognition and cancer treatment that are difficult to detect in behavioral outcomes. Cognitive deficits in BCS have primarily been identified in domains of verbal and visuospatial ability [36]; thus, the lack of differences in performance on the flanker task, a measure of interference control, supports domain-specific cancer-related cognitive impairments. Another possible explanation for a lack of differences in cognitive performance is that BCS may have recovered from any cognitive deficits resulting from treatment. In our sample of BCS, time since treatment ranged from 2 to 33 months. Although there is evidence of cognitive deficits as long as 20 years after completion of cancer treatment [41, 42], longitudinal

Table 4 Summary of multilevel regression analyses predicting flanker incompatible task performance

	Congruent			Incongruent			
	Accuracy[a]	RT[a]		Accuracy[b]		RT[c]	
Parameters *Est. (SE)*	Fruit	Fruit	Vegetable	Fruit	Vegetable	Fruit	Vegetable
Intercept	92.79 (1.79)***	458.52 (13.02)***	463.33 (12.91)***	89.28 (1.91)***	88.43 (2.09)***	490.83 (12.75)***	497.48 (12.43)***
Group	−3.34 (2.53)	1.84 (18.45)	−8.28 (18.27)	.08 (2.68)	1.73 (2.95)	−8.93 (18.08)	−22.02 (17.62)
Age	–	–	–	−.44 (.15)**	−.38 (.16)*	2.79 (.97)**	2.77 (.94)**
Education	2.20 (1.15)	−18.69 (8.37)*	−21.68 (8.06)**	–	–	−20.51 (8.23)*	−24.08 (7.77)**
Fruit	8.27 (3.08)**	−49.67 (22.51)*	–	13.28 (3.27)**	–	−62.08 (22.46)**	–
Vegetable	–	–	−30.15 (12.56)*	–	4.11 (2.06)*	–	−40.71 (12.23)**
Pseudo R^2	.21	.18	.19	.27	.12	.30	.33

Dashes in cells indicate excluded variables not entered into the model

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

[a] Variables excluded ($p > 0.1$): age, income, BMI, cancer stage, time since cancer diagnosis, treatment (radiation, chemotherapy, radiation + chemotherapy, aromatase inhibitor, selective estrogen receptor modulator)

[b] Variables excluded ($p > 0.1$): education, income, BMI, cancer stage, time since cancer diagnosis, treatment (radiation, chemotherapy, radiation + chemotherapy, aromatase inhibitor, selective estrogen receptor modulator)

[c] Variables excluded ($p > 0.1$): income, BMI, cancer stage, time since cancer diagnosis, treatment (radiation, chemotherapy, radiation + chemotherapy, aromatase inhibitor, selective estrogen receptor modulator

studies have identified remissions in cognitive impairment 6–18 months after completion of chemotherapy [43–45]. Approximately 75 % of breast cancer patients report some impact on cognitive functioning during treatment [6, 7]; therefore, future studies should consider investigating cognitive deficits during treatment when the highest rates of cognitive impairment are reported.

Our second aim was to explore the potential role of diet as a moderator of cognitive function. The current study provided novel evidence relating diet to interference control among women with and without a history of breast cancer. Interference control is an important component of cognitive control that reflects the ability to inhibit irrelevant aspects of the environment and focus attention toward relevant aspects of the environment. For example, when driving, interference control is required to attend to other vehicles and pedestrians rather than advertising signage on the side of the roadway. Fruit intake and vegetable intake were associated with better performance (i.e., shorter RT and better accuracy) on the flanker task, regardless of disease status. Interestingly, the association between dietary components and cognition was stronger for the incompatible condition, which required greater demand for interference control than the compatible condition, suggesting that fruits and vegetables may be important for the upregulation of interference control when faced with higher cognitive demands. Fruits and vegetables contain an array of micronutrients and phytochemicals that may elicit neuroprotection by modulation of pathways implicated in the pathogenesis of cognitive impairment and dementia. In particular, fruits and vegetables are rich sources of flavonoids, which have been shown to inhibit neuroinflammation and neurodegeneration, stimulate brain blood flow, and induce neurogenesis [23]. Fruits and vegetables are also sources of soluble fiber that can be fermented to produce short-chain fatty acids (SCFAs), which may elicit cognitive benefits. A diet containing 10 % pectins decreased markers of neuroinflammation in mice [46], and sodium butyrate, a derivate of the SCFA butyrate, has been demonstrated to restore learning and memory in mouse models of neurodegeneration [47, 48]. Further research should investigate which subgroups of fruits and vegetables are most protective, as there is evidence that nutrient- and phytochemical-rich vegetables such as green leafy vegetables, cruciferous vegetables, citrus fruits, and yellow vegetables elicit greater health benefits [16, 49, 50].

The strengths of this study include the use of validated measures of interference control and diet intake. Furthermore, the BCS and age-matched controls were similar in demographic variables, BMI, and dietary intake; therefore, comparisons of cognitive function between these groups were not confounded by differences in these covariates known to impact cognitive function. We believe this is also one of the first studies to examine cognitive function and nutrition in BCS. However, there were also important limitations in this study. Although the sample is relatively small, the study served as hypothesis building in the area of nutrition and cognitive function in BCS. Furthermore, our sample size is comparable to other studies examining cancer-related cognitive impairment in BCS [39, 41, 51]. Due to the small sample size and cross-sectional nature of the study, our results may be confounded by several variables that were not adjusted for in our analysis including cancer stage, treatment regimens, time since diagnosis, and psychological measures such as fatigue, anxiety and depression. Additionally, the small sample and limited variability in dietary intake between subjects limited the ability to identify the impact of other dietary components on cognitive function. Furthermore, 3-day food records are a measure of recent usual intake, and not habitual dietary intake. The majority of our sample were white, married, highly educated, and higher socioeconomic status; thus, the application of our findings to other populations is limited. BCS were not evaluated prior to treatment, so it is unknown whether current cognitive function reflects a decline from pre-diagnosis and treatment status. Despite the limitations in this study, our findings provide a foundation for the future investigation of the effects of dietary intake on cancer-related cognitive impairment.

In summary, there was no difference in performance on an interference control task between BCS and age-matched controls. However, higher intake of fruit or vegetables were predictive of better interference control in both BCS and age-matched controls. This is the first study, to our knowledge, to identify a positive association between a dietary pattern consisting of fruits and vegetables and cognitive performance in BCS. There is a significant body of evidence that suggests a dietary pattern high in fruits and vegetables is associated with many positive health outcomes, and this study highlights the need for further research to identify dietary components that promote cognitive health, particularly in populations at risk for cancer-related cognitive impairment.

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Compliance with Ethical Standards

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the University of Illinois Institutional Review Board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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