



Characteristics of cancer patients participating in presurgical lifestyle intervention trials exploring effects on tumor biology



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ABSTRACT

Background: Poor diet and insufficient physical activity are strongly associated with an increased risk of several cancers. Preclinical studies suggest that lifestyle modifications may exert favorable effects on tumor biology. Randomized controlled trials in the presurgical setting serve as an ideal means to translate this research to humans; however, little is known about the characteristics of patients who enroll in these presurgical trials versus those who do not.

Methods: Screening databases from three presurgical lifestyle intervention trials for breast and prostate cancer patients conducted at Duke University Medical Center (NCT00049309) and the University of Alabama at Birmingham (NCT02224807 and NCT01886677) were combined for analysis. Demographic and anthropometric differences between enrolled vs. non-enrolled individuals were assessed using Chi-square for categorical variables and t-tests for continuous variables.

Results: There was no difference in participation rate when comparing minority status or overweight and obese patients. However, obese females were slightly more likely to enroll than women who were overweight ($p = 0.110$), a trend not seen in men. Women were also less likely than men to participate if their study site was > 25 miles from their home ($p = 0.034$). Patients who had completed a college degree were somewhat less likely to enroll than those with less educational attainment ($p = 0.072$). Of those who did not enroll, 80% cited a lack of time.

Conclusion: Similar to other clinical trials, lack of time is a leading barrier to enrollment, and travel/distance appears to be a greater barrier for women in presurgical studies. Larger presurgical lifestyle intervention trials will require tailored strategies to enhance recruitment.

1. Introduction

Obesity and lifestyle factors, such as diet and insufficient physical activity, serve as risk factors for 13 types of cancer and as prognostic indicators for 15 different malignancies [1,2]. Animal models have demonstrated that energy restriction positively impacts tumor biology, and similar findings have been reported for dietary modification and increased physical activity [3,4]. Translational trials during the presurgical period serve as a valuable bridge that could improve patient outcomes and inform future clinical practice; however, few have been conducted to date.

Currently, there are over 15 million Americans who are living beyond a cancer diagnosis. Of this large patient population, it is estimated that only 3–4% (450,000–600,000) of eligible adult patients will enroll in a non-therapeutic or behavioral clinical trial during active treatment

[5]. When questioned regarding reasons for not enrolling in a clinical trial, most adult cancer survivors cited lack of information about available trials as their primary reason for not enrolling. Secondary reasons included fear of reduced quality of life and the belief that insurance would not cover costs [6]. Within the population of adults who enroll, an even smaller fraction will participate in lifestyle intervention trials exploring effects on tumor biology during the presurgical period because opportunities are currently limited.

By pooling data from multiple studies, we aim to compare the characteristics of adult cancer patients who enroll in presurgical trials versus those electing not to enroll. This information will help researchers better understand the barriers in trial enrollment, inform recruitment strategies for future trials, and minimize patient drop-out. It is hypothesized that participants in presurgical trials will differ from nonparticipants in race, educational attainment, body mass index

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Table 1
Study summary.

Disease Site	Recruitment Sites	Targeted Accrual (Actual Accrual) (n)	Screened (N)	Attrition (%)	Variables Collected	Exclusion Criteria
Prostate	- Duke University Medical Center - Durham Veteran's Administration - University of Michigan Community Clinical Oncology Program	160 (161) ^a	531	7.5	- Age - Ethnicity - Education level	- Surgery < 21 days away - Recent flaxseed use - Current diet ≤30% kcal from fat - Began dietary supplements in last 3 months - Current antibiotic use - Previous history of chemotherapy
Prostate	- University of Alabama at Birmingham - Urology Centers of Alabama	40 (40)	101	15.0	- Age - Ethnicity - BMI - Distance from center - Refusal reason	- Non-English speaker - Surgery < 23 days away - Previous history of chemotherapy - Other active malignancy - Current medical condition affecting weight - Current medical condition precluding exercise - Currently enrolled in a weight loss program
Breast	- University of Alabama at Birmingham - Kirklin Breast Clinic	40 (33) ^a	100	0	- Age - Ethnicity - BMI - Distance from center - Refusal reason	- Non-English speaker - Surgery < 21 days away - Other active malignancy - Current medical condition affecting weight - Current medical condition precluding exercise - Currently enrolled in a weight-loss program - Non-English speaker

^a Follow-up discontinued due to advanced disease and subsequent ineligibility.

(BMI), and distance from their respective study sites.

2. Patients and methods

Data were obtained from three individual studies conducted at Duke University and the University of Alabama at Birmingham to form an overall study population of 731 patients [3,4,7]. The characteristics of the individual studies are represented in Table 1. Patients were recruited in coordination with cancer treatment teams. Individuals who met eligibility criteria with regard to cancer stage were approached. Educational attainment was self-reported; race and distance from study site were obtained from medical record. Both trials performed at UAB [3,4] had a requisite BMI ≥ 25, while this information was not collected during screening in the trial at Duke. Available BMIs (n = 194) were categorized as overweight (25–29.9 kg/m²) and obese (BMI ≥ 30 kg/m²).

Race was dichotomized as non-Hispanic white and minority, which included non-Hispanic black (n = 186), Hispanic (n = 8), Asian/Pacific Islander (n = 5), Native American (n = 13), and other (n = 1). Education was categorized two ways based on distribution; for the first, less than high school graduate and high school graduate were combined, some college and tech/trade school were combined, and college graduate and post graduate degree were combined. For the alternate categorization, education was dichotomized by those who did not graduate college vs. those who graduated.

Statistical analyses were performed using SPSS Statistics Version 24.0 (IBM Corp, Armonk, NY, USA). Differences in demographic and anthropometric measures between those who enrolled and those who did not were assessed using Chi-square tests for categorical variables and t-tests for continuous variables. Additional analyses investigated gender differences in participation rate by the other categorical variables using identical analytical methods.

3. Results

Results of this study are summarized in Table 2. The proportion of

minorities within the pool of available patients was 33%, which is representative of the southeastern US where both Duke and UAB are located [8]. No differences were observed in rates of enrollment between minority and non-minority patients.

A total of 632 men were screened for the two prostate cancer studies and 100 women were screened for the breast cancer study. Enrollment ratios were similar for male and female participants. Among participants in the UAB trials, no differences in BMI were found when enrolled patients were compared to those who chose not to enroll. It was observed, however, that obese females, but not males, were more likely to enroll than those who were overweight (p = 0.110 and p = 0.834 for females and males, respectively). Also, female patients who lived > 25 miles away from the study site were significantly less likely to enroll in the trial unlike males (p = 0.034 and p = 0.184 for females and males, respectively), though there was no difference overall in enrollment rates by distance.

Educational attainment was somewhat predictive of enrollment, as those who completed college were slightly less likely to enroll than those with less education (p = 0.072). Of those who did not enroll, 80% cited a lack of time, though post-hoc analysis suggests that this reason for refusal was not associated with any traits previously mentioned. Other barriers were the desire to focus on their primary cancer care (5%), and distance (3%).

4. Discussion and conclusion

This is the first study to investigate the characteristics of cancer patients recruited into presurgical lifestyle intervention trials. In this pooled analysis, we observed some indication that those of higher educational attainment were less likely to participate, and that weight status and distance were significantly associated with enrollment of female participants, but not males.

Although more highly-educated individuals reported a 3–4 fold greater awareness of clinical trials [9], our data suggest that those who were more highly educated were somewhat less likely to participate in presurgical trials than those with less education (p = 0.072). While

Table 2
Characteristics of enrolled vs. not enrolled cancer patients in presurgical lifestyle intervention trials.

		Enrolled		Did Not Enroll		p-value
		n	%	n	%	
Gender ^a	Male	201	86.3	431	86.4	1
	Female	32	13.7	68	13.6	
Race ^b	Minority	77	33	136	27.4	0.117
	Non-Hispanic	156	67	361	72.6	
	White					
DCIS	Minority	15	46.9	23	33.8	0.270
	Non-Hispanic	17	53.1	45	66.2	
	White					
R21 Prostate	Minority	13	32.5	16	26.2	0.509
	Non-Hispanic	27	67.5	45	73.8	
	White					
Flax	Non-Hispanic	77	33	136	27.4	0.343
	White					
BMI ^c	Minority	156	67	361	72.6	0.444
	Overweight	24	33.3	48	39.3	
DCIS	Obese	48	66.7	74	60.7	0.110
	Overweight	7	21.9	26	40	
R21 Prostate	Obese	25	78.1	39	60	0.834
	Overweight	17	42.5	22	38.6	
Distance from Center ^d	Obese	23	57.5	35	61.4	0.344
	Overweight	17	42.5	22	38.6	
All	Mean (SD)	46	(60.1)	54.4	(58.4)	0.052
	< 25 Miles	32	59.3	49	48.5	
	≥ 25 Miles	22	40.7	52	51.5	
DCIS	< 25 Miles	26	83.9	40	60.6	0.034
	≥ 25 Miles	5	16.1	26	39.4	
R21 Prostate	< 25 Miles	16	41	15	26.8	0.184
	≥ 25 Miles	23	59	41	73.2	
Educational Attainment ^e	Flax					0.113
	≤ HS	42	27.1	83	26.2	
	Some	46	29.7	69	21.8	
	College + Tech					0.072
	College Grad +	67	43.2	165	52.1	
	Less than College	88	56.8	152	47.9	
Grad						
College Grad +	67	43.2	165	52.1		

^a n = 233 for enrolled, n = 499 for not enrolled.

^b n = 233 for enrolled, n = 497 for not enrolled.

^c n = 72 for enrolled, n = 122 for not enrolled.

^d n = 70 for enrolled, n = 122 for not enrolled.

^e n = 155 for enrolled, n = 317 for not enrolled.

each of these studies provided reimbursement for mileage and parking, we anticipated that the lost time from work or home would be a greater barrier to less-educated individuals who were more apt to hold blue-collar positions than those with higher educational attainment and flexibility. However, this was not the case. Nor did we observe enrollment differences by race, similar to the findings of Igwe et al. in a study of gynecologic oncology patients [10].

Higher enrollment rates were seen among obese women than in overweight women; however, this trend was not observed in men. This disparity may be due to evidence that women of all ages have been found to be more concerned with body weight and appearance than men [11]. Heightened awareness of obesity-related health risks, particularly right before surgery, also may be a persuading influence for participation. Whether oncologists played a role in conveying this information during recruitment for these studies is unknown; however, the role of the physician in encouraging patient participation is crucial [12].

The increased likelihood of male participants to travel farther than females may stem from a difference in attitudes towards driving. Hempel et al. found that among 2473 adults aged 55–70 (similar age as those recruited into each of these trials), women were significantly more likely to report driving anxiety than men [13].

Of note, the presurgical trials analyzed herein required that some participants delay their surgeries, as all studies required a minimum 21 days for the intervention. This concern has been previously cited as a reason for non-enrollment by Abraham et al. [14], and may have increased the number of patients who chose not to enroll, as they were reluctant to change their plan of treatment. That being said, a major reason for incompletion of presurgical trials was the cancellation of surgery. This was particularly noteworthy in prostate cancer – a cancer for which numerous treatment options exist, many of which are associated with a lower prevalence of side effects [15]. Future presurgical trials should factor this in.

While the importance of presurgical translational trials is unquestioned, many barriers to recruitment have limited their use. These barriers include patients who do not wish to delay treatment or who are overwhelmed or reluctant to assume additional responsibilities while they prepare for surgery [3]. Moreover, strategies for active surveillance employed in several types of cancers including prostatic carcinoma and in situ cancers also reduce the pool of potential recruits available for presurgical trials [3]. For these reasons, only five lifestyle intervention trials with a specific focus on tumor biology in the presurgical setting have been completed to date. The largest of these studies (n = 161) investigated the effects of supplemental flaxseed on tumor proliferation rates and found a significant decrease in tumor Ki-67 with supplementation [7]. Smaller studies were undertaken by Schenk et al. (n = 4) and Wright et al. (n = 9) and observed that short term negative energy balance reduced body weight and levels of growth hormones in the serum [16,17]. Most recently, two pilot studies investigated the effects of negative energy balance on tumor Ki-67 and other biomarkers associated with malignancy in prostate (n = 40) and breast (n = 33) cancers [4,18]. These trials proved to be feasible but must be replicated to advance translational science.

Overall, the retention of individuals in these presurgical trials was excellent; eighteen individuals in total dropped-out across all studies; i.e., six drop-outs in the prostate cancer weight loss trial, and 12 drop-outs in the flaxseed trial (Table 1). Issues with surgery were the leading reason for drop-out with 14 men cancelling their prostatectomy, and two men not completing the trial because their surgery was either moved-up or delayed. Other reasons for drop-out were dissatisfaction with randomization assignment to the control arm (one man in the weight loss trial); and subsequent identification of metastatic disease (one man in the weight loss trial). Drop-outs did not differ from completers by education or race.

While this is the first study to investigate factors associated with participation in presurgical trials, there are some limitations. First, only two cancer types were investigated due to the limited availability of study data specific to the presurgical patient population. Second, variables were not consistent between databases (i.e., distance and education) which limited the sample size in several analyses. Also, all studies were conducted in the southeastern United States, which may not be representative of other regions. Nonetheless, these findings indicate opportunities for tailoring recruitment to different demographic groups, including involvement of the cancer treatment team. Presurgical trials are needed to better understand the effects of lifestyle modification on tumor biology; increased collaboration and resources may be necessary to achieve enrollment numbers sufficient to translate preclinical findings.

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