Outcomes of a cluster randomized trial in young breast cancer survivors and blood relatives: surveillance and genetic services

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Key words: statewide random sampling, cancer survivorship, cancer surveillance, HBOC, genetic testing, targeted intervention, tailored intervention

ABSTRACT

We compared the efficacy of a tailored and a targeted intervention designed to increase clinical breast exam (CBE), mammography, and genetic services/testing among young breast cancer survivors (YBCS) (diagnosed <45 years old) and their blood relatives. A two-arm cluster randomized trial recruited a random sample of YBCS from the Michigan cancer registry and up to two of their blood relatives. Participants were stratified according to race and randomly assigned as family units to the tailored (n=637) or the targeted (n=595) intervention. Approximately 40% of participants were Black; 12% YBCS and 27% relatives were living in more than 20 different U.S. States. Higher screening rates were reported by YBCS (CBE p=0.05; mammography p=0.04) and relatives (CBE p<0.01; mammography p=0.04) in the tailored arm, and by White/Other YBCS (CBE p=0.02) and relatives (CBE p<0.01; mammography p=0.03). YBCS genetic testing rates increased from 22% to 26% (p=0.11). Black YBCS and relatives reported higher self-efficacy and intention for genetic testing, and higher satisfaction and intervention acceptance. The tailored intervention improved CBE and mammography uptake - despite having minimal contact with participants. Professional referrals will improve genetic testing uptake. Intervention materials increased self-efficacy and satisfaction for Black women but could not overcome multiple access barriers.

Word count: 200

Keywords: HBOC, statewide random sampling, cancer survivorship, targeted intervention, tailored intervention, Black participants, family recruitment

INTRODUCTION

About 25% of new breast cancer cases are diagnosed in young women (young breast cancer survivors - YBCS) who are more likely to carry germline pathogenic variants associated with hereditary breast and ovarian cancer (HBOC) syndrome [1,2]. National guidelines for YBCS recommend annual clinical breast exams (CBE) and mammograms to screen for local recurrence or a new primary breast cancer, and genetic services (counseling and testing)[3,4]. However, there is documented underutilization of mammography surveillance and cancer genetic services in YBCS[5-8], especially among Black women[9-12], primarily due to lack of awareness and/or lack of access to genetic testing[13,14]. First- and second-degree relatives of YBCS have a 2.3 and 1.5 increased relative breast cancer risk, respectively[15], however, they may not always manage this risk effectively due to lack of information, limited family communication, or inaccurate understanding of cancer risk inheritance patterns[16-18].

Informing YBCS and relatives about their cancer risk and surveillance guidelines can improve cancer survival. However, only few studies have addressed this gap. A prior randomized clinical trial (RCT) compared the efficacy of telephone versus in person genetic counseling in breast cancer patients and cancer-free relatives who were recruited from a population-based database and a cancer registry [19]. Although in-person counseling led to higher uptake of genetic testing at 1-year follow-up, both methods were acceptable in disseminating information about screening guidelines [20]. A second RCT tested the efficacy of telephone counseling versus a brochure to increase genetic testing among women recruited through a statewide telephone service. Within 60 days the percentage of women tested was similar for both interventions [21]. A limitation of these two RCTs was that they included less than 10% of Black women. Moreover, although in-person and telephone counseling strategies are the most personalized forms of contact [22], they require more costly professional resources to increase guideline-based cancer surveillance and genetic testing.

The present study compared the efficacy of a *targeted* versus a *tailored* intervention delivered by postal mail to CBE, mammography screening, and use of genetic testing that is consistent with National Comprehensive Cancer Network (NCCN) screening guidelines in YBCS and blood relatives. We also examined self-efficacy and intention to perform these behaviors. We addressed prior translational gaps by developing less costly strategies for remote intervention delivery, oversampling for Black participants, and assessing participants' satisfaction and acceptance of the interventions.

Interventions

The Theory of Planned Behavior (TPB)[23] guided the development of the *targeted* and the *tailored* intervention (**Table 1**). The **targeted** intervention included a letter and a booklet written at the seventh grade reading level providing information about genetic counseling, cost, and a list of certified cancer genetic services in the state of Michigan. The booklet presented mammography screening as more sensitive than CBE and more accessible compared to MRI[24], and different options for low cost mammograms. The targeted letter included the name of the participant and recommended that she sought genetic evaluation and appropriate breast cancer surveillance/screening due to her own or her relative's early age of cancer onset.

The **tailored** intervention included the same targeted booklet as above and a second booklet encouraging participants to seek support from their family members in order to pursue breast cancer screening and genetic services. A computer algorithm generated a letter, which provided tailored feedback based on participant's responses to the baseline survey on cancer surveillance/ screening and genetic testing outcomes. For example, if an YBCS reported that she did not have a mammogram for more than 12 months due to cost-related access to care, the letter encouraged her to seek a low cost mammogram from resources listed in the booklet.

Table 1. Elements of the tailored and the targeted interventions

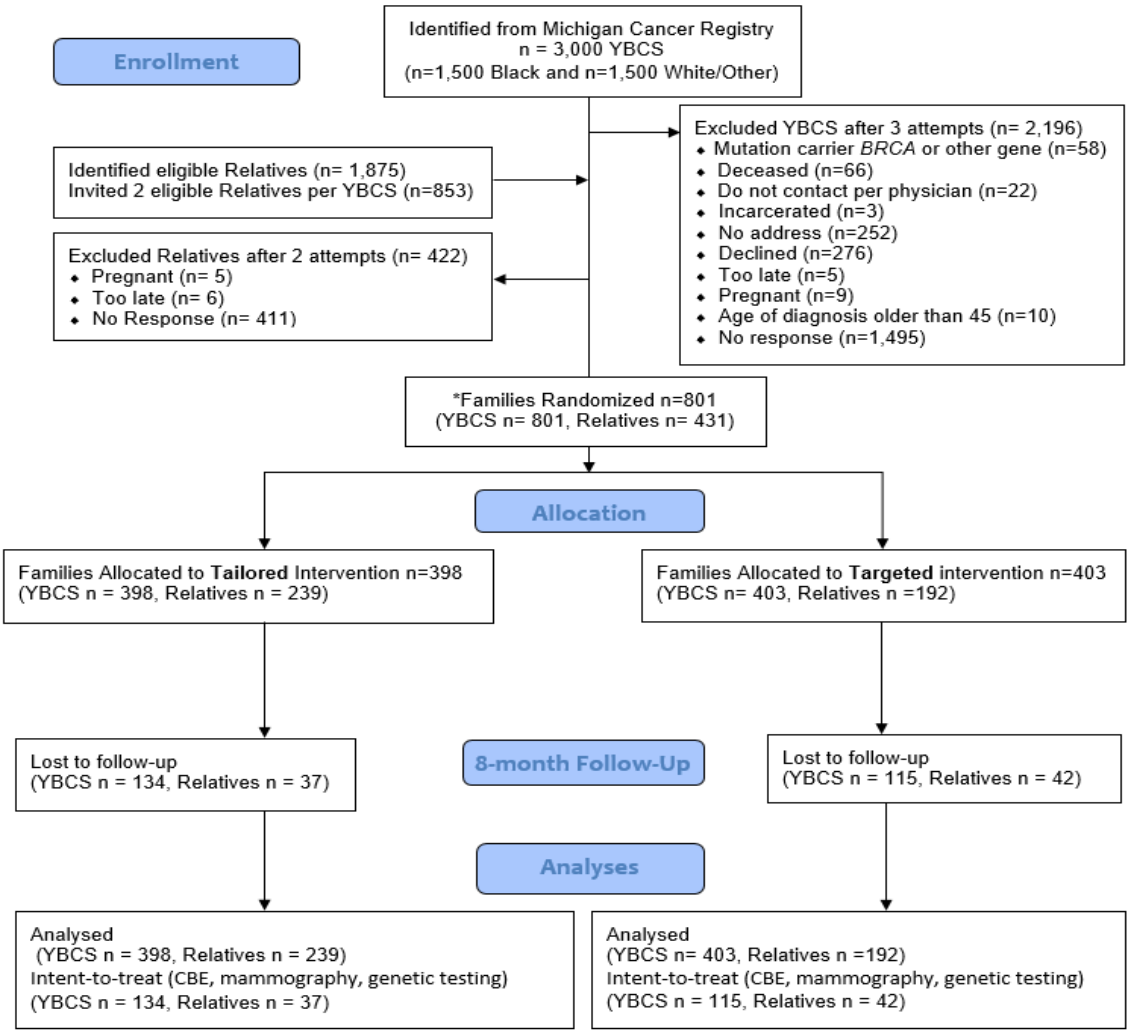
<table>
<tr><th colspan="2">Tailored Intervention</th><th colspan="2">Targeted Intervention</th></tr>
<tr><td colspan="2">Booklet 1 – Surveillance and Genetic Testing</td><td colspan="2">Booklet 1 – Surveillance and Genetic Testing</td></tr>
<tr><td colspan="2">• Risk factors and cancer genetics</td><td colspan="2">• Risk factors and cancer genetics</td></tr>
<tr><td colspan="2">• Genetic counseling, cost</td><td colspan="2">• Genetic counseling, cost</td></tr>
<tr><td colspan="2">• Certified genetic services in MI</td><td colspan="2">• Certified genetic services in MI</td></tr>
<tr><td colspan="2">• Breast cancer surveillance</td><td colspan="2">• Breast cancer surveillance</td></tr>
<tr><td colspan="2">• Low cost mammograms</td><td colspan="2">• Low cost mammograms</td></tr>
<tr><td colspan="2">Booklet 2 – Family Support</td><td colspan="2" rowspan="3"></td></tr>
<tr><td colspan="2">• Cancer and open family communication</td></tr>
<tr><td colspan="2">• Family support in illness</td></tr>
<tr><td colspan="2">Tailored Letter</td><td colspan="2">Targeted Letter</td></tr>
<tr><td>YBCS</td><td>Relatives</td><td>YBCS</td><td>Relatives</td></tr>
<tr><td>• Participant’s name</td><td>• Participant’s name</td><td>• Participant’s name</td><td>• Participant’s name</td></tr>
<tr><td>• Surveillance according to guidelines for follow-up care</td><td>• Screening according to guidelines for breast cancer</td><td>• Increased risk - early age of cancer onset</td><td>• Increased risk - family history of early age of cancer onset</td></tr>
<tr><td>• Barriers/facilitators to follow-up care</td><td>• Barriers/facilitators to breast cancer screening</td><td>• NCCN guidelines for follow-up care</td><td>• NCCN guidelines for breast cancer surveillance</td></tr>
<tr><td>• Barriers/facilitators to genetic services</td><td>• Barriers/facilitators to genetic services</td><td>• Suggest genetic evaluation</td><td>• Suggest genetic evaluation</td></tr>
<tr><td>• Fear of cancer recurrence</td><td>• Gail and Claus risk score</td><td colspan="2" rowspan="4"></td></tr>
<tr><td>• Genetic literacy (breast cancer risk factors and inheritance)</td><td>• Genetic literacy (breast cancer risk factors and inheritance)</td></tr>
<tr><td>• Family communication</td><td>• Family communication</td></tr>
<tr><td>• Family support in illness</td><td>• Family support in illness</td></tr>
</table>

Elements of both interventions

RESULTS

Study enrollment, randomization and retention data are shown in the CONSORT diagram **(Figure 1)**. Among 859 eligible YBCS who accepted participation, 58 reported either carrying a previously detected pathogenic variant associated with HBOC and/or having a hereditary cancer syndrome (e.g., Li Fraumeni) excluding them from the RCT. Response rates were 38.6% for White/Other YBCS and 27.5% for Black YBCS. YBCS identified 1,875 eligible relatives and they were willing to contact 1,360 (72.5%) of them. The study invited up to two relatives per YBCS (total n=853) and of these n=442 (51.5%) accepted participation. Among YBCS 11.9% resided in 23 U.S. States other than Michigan; among relatives 27.4% resided in 27 other states.

Figure 1. Consort diagram



*Stratified randomization of YBCS according to race (Black vs. White/Other); relatives would follow randomized arm of YBCS

After randomization, YBCS in both study arms did not differ at baseline (**Table 2**). YBCS were on average 51 years old and were diagnosed on average 40 years old; approximately one in five had more than one cancer diagnoses[25]. Relatives were on average 44 years old. Relatives in the tailored arm reported more comorbidities, and relatives in the targeted arm reported a higher annual household income. These differences were not observed in the follow-up survey. Approximately one in five YBCS and one in five relatives reported cost-related lack of access to healthcare. Follow-up surveys were received from 610 YBCS (76.2% retention) and 352 relatives (81.7% retention).

Table 2. Demographic characteristics and barriers by intervention arm

YBCS		Baseline (n=801)		Follow-up (n=610)	
		Tailored (n=398)	**Targeted (n=403)**	**Tailored (n=295)**	**Targeted (n=315)**
ANTECEDENTS	Age	51.11± 5.76 (25 – 64)			
	Race (Black %)	162 (40.70%)	162 (40.20%)	98 (33.22%)	116 (36.83%)
	Education <= High School	85 (21.36%)	103 (25.56%)	65 (22.03%)	78 (24.76%)
	Caregiving responsibilities	120 (30.15%)	141 (34.99%)	71 (24.07%)	89 (28.25%)
	Anxiety	102 (25.63%)	122 (30.27%)	80 (27.12%)	94 (29.84%)
	Depression	109 (27.39%)	116 (28.78%)	91 (30.85%)	91 (28.89%)
	Comorbidities	252 (63.32%)	277 (68.73%)	190 (64.41%)	211 (66.98%)
BARRIERS	Income≤ $40,000	118 (29.65%)	124 (30.77%)	90 (30.51%)	95 (30.16%)
	No insurance	30 (7.54%)	22 (5.46%)	15 (5.08%)	17 (5.40%)
	No routine source of care	23 (5.78%)	33 (8.19%)	20 (6.78%)	16 (5.08%)
	Cost-related lack of access	73 (18.34%)	71 (17.62%)	42 (14.24%)	43 (13.65%)
	Mean distance to closest genetic center (miles)	18.58± 26.48 (0-147.6)	19.51± 27.38 (0-147.6)	18.58± 26.45 (0-147.6)	19.24± 27.10 (0-147.6)
RELATIVES		**Baseline (n=431)**		**Follow-up (n=352)**	
		Tailored (n=239)	**Targeted (n=192)**	**Tailored (n=202)**	**Targeted (n=150)**
ANTECEDENTS	Age	43.36±11.88 (25 – 64)			
	Race (Black %)	46 (19.25%)	41 (21.35%)	33 (16.34%)	32 (21.33%)
	Education ≤ High School	40 (16.74%)	32 (16.67%)	33 (16.34%)	27 (18.00%)
	Caregiving responsibilities	105 (43.93%)	80 (41.67%)	87 (43.07%)	58 (38.67%)
	Anxiety	72 (30.13%)	43 (22.40%)	55 (27.22%)	34 (22.67%)
	Depression	62 (25.94%)	49 (25.52%)	54 (26.73%)	42 (28.00%)
	Comorbidities	**138 (57.74%)**	**92 (47.92%)**	115 (56.93%)	76 (50.67%)
BARRIERS	Income≤ $40,000	**65 (27.20%)**	**70 (36.46%)**	63 (31.19%)	55 (36.67%)
	No insurance	33 (13.81%)	23 (11.98%)	16 (7.92%)	16 (10.67%)
	No routine source of care	30 (12.55%)	16 (8.33%)	20 (9.90%)	9 (6.00%)
	Cost-related lack of access	52 (21.76%)	30 (15.63%)	42 (20.79%)	28 (18.67%)
	Mean distance to closest genetic center (miles)	21.16± 31.09 (0-196.7)	25.44± 33.41 (0-195.9)	21.16± 31.09 (0-196.7)	25.69± 33.65 (0-195.9)

Bold=significant difference ≤ 0.05

Breast cancer screening and genetic testing

Table 3 presents outcomes from the baseline and the follow-up survey for YBCS' and relatives' CBE, mammograms, and genetic testing. CBE and mammography were categorized as consistent or non-consistent with 2013 NCCN surveillance recommendations, which were relevant at the time of the study[26]. Approximately 80% of YBCS and 70% of relatives reported CBE and mammograms consistent with NCCN guidelines at baseline. Genetic testing was reported by 23% of YBCS and 3% of relatives. In the 8-month follow-up survey approximately 90% of YBCS and 82% of relatives reported having had CBE and mammograms consistent with NCCN guidelines, representing approximately 10% increase from baseline. In the follow-up survey approximately 28% YBCS and 5% relatives reported having genetic testing. There were 40 new YBCS and 9 new relative cases who reported having genetic testing between the baseline and the follow-up survey. Comparisons between the two interventions did not identify significant differences in outcomes. However, within group comparisons showed that YBCS and relatives in the tailored arm were significantly more likely to report higher CBE and mammography rates. Relatives in the tailored arm were also more likely to report having genetic testing and greater self-efficacy for CBE (p=0.0135).

Table 3. CBE, mammography, and genetic testing for the two intervention arms

Outcomes for YBCS	Baseline		Follow-up (ITT)*		Between Groups Tailored vs. Targeted p	Within Group Follow-up vs. Baseline p	
	Tailored	Targeted	Tailored	Targeted		Tailored	Targeted
CBE –NCCN Guidelines	342	333	361	356	0.66	**0.05**	**0.03**
Tailored (n=398) Targeted (n=403)	(85.92%)	(82.63%)	(90.70%)	(88.33%)			
Mammography[1] –NCCN Guidelines	298	292	315	302	0.25	**0.04**	0.27
Tailored (n=340) Targeted (n=335)	(87.64%)	(87.16%)	(92.65%)	(90.15%)			
Had Genetic Testing	79	107	99	127	1.00[#]	0.11[#]	0.14[#]
Tailored (n=398) Targeted (n=403)	(19.85%)	(26.55%)	(24.87%)	(31.52%)			
Outcomes for Relatives	**Baseline**		**Follow-up (ITT)***		**Between Groups Tailored vs. Targeted p**	**Within Group Follow-up vs. Baseline p**	
	Tailored	**Targeted**	**Tailored**	**Targeted**		**Tailored**	**Targeted**
CBE –NCCN Guidelines	179	146	204	161	0.44	**0.01**	0.07
Tailored (n=239) Targeted (n=192)	(74.89%)	(76.04%)	(85.36%)	(83.85%)			
Mammography[2] –NCCN Guidelines	109	87	126	96	0.43	**0.04**	0.24
Tailored (n=156) Targeted (n=122)	(69.87%)	(71.31%)	(80.77%)	(78.69%)			
Had Genetic Testing	9	4	17	5	0.08[#]	0.16[#]	1[#]
Tailored (n=239) Targeted (n=192)	(0.04%)	(0.02%)	(0.07%)	(0.03%)			

* Intention to Treat

[#] Fischer Exact Test

1. Excludes YBCSs with double mastectomy
2. Excludes relatives younger than 35 years old AND relatives between 35 to 40 with Gail lifetime risk <20% according to NCCN guidelines

Bold= significant difference ≤ 0.05

We examined how each co-variable influenced within-group intervention effects (follow-up minus baseline scores), after controlling for all other co-variables at baseline. Self-efficacy for genetic testing increased among YBCS in the tailored arm (p=0.0205). Intention for genetic testing increased among older (p=0.0002) and Black (p=0.0000) YBCS, those with fewer cost-related barriers accessing care (p=0.0001), and lived closer to genetic services (p=0.0000). YBCS needing less support from providers reported higher self-efficacy for CBE (p=0.0070) and genetic testing (p=0.0020), and intention for CBE (p=0.007), mammography (p=0.0323) and genetic testing (p=0.0000). Fewer barriers for mammography were reported from YBCS with higher education (p=0.0024), those living further from healthcare services (p=0.0072), and those with higher family coherence (p=0.0034). Self-efficacy for genetic testing increased among Black relatives (p=0.0210). Relatives needing less support from providers reported higher self-efficacy (p=0.0016) and intention for genetic testing (p=0.0048). Older relatives reported higher self-efficacy (p=0.0329) and intention (p=0.0089) for mammography. Relatives with fewer cost-related barriers accessing care reported higher intention for mammography (p=0.0258).

Table 4 compares intervention outcomes for Black and White/Other YBCS and relatives. Between groups comparisons did not identify significant differences in outcomes. However, within group comparisons showed that White/Other YBCS and White/Other relatives were significantly more likely to report higher CBE and mammography rates. They were also more likely to report having genetic testing, but statistically significant differences were not identified due to small numbers.

Table 4. CBE, mammography, and genetic testing for Black and White/Other participants

Outcomes for YBCS	Baseline		Follow-up (ITT)*		Between Groups Black vs. White/Other p	Within Group Follow-up vs. Baseline p	
	Black	White/Oher	Black	White/Other		Black	White/Other
CBE –NCCN Guidelines	268	407	286	431	0.88	0.06	**0.02**
Black (n=324) White/Other (n=447)	(82.72%)	(85.32%)	(88.27%)	(90.36%)			
Mammography[1] –NCCN Guidelines	244	346	259	360	0.49	0.10	0.08
Black (n=293) White/Other (n=382)	(83.28%)	(90.58%)	(88.40%)	(94.24%)			
Had Genetic Testing	52	134	68	158	1[#]	0.13[#]	0.11[#]
Black (n=324) White/Other (n=477)	(16.05%)	(28.09%)	(20.99%)	(33.12%)			
Outcomes for Relatives	**Baseline**		**Follow-up (ITT)***		**Between Groups Tailored vs. Targeted p**	**Within Group Follow-up vs. Baseline p**	
	Black	**White/Other**	**Black**	**White/Other**		**Black**	**White/Other**
CBE –NCCN Guidelines	63	262	71	294	1	0.21	**<0.01**
Black (n=87 White/Other (n=344)	(72.41%)	(76.16%)	(81.61%)	(85.47%)			
Mammography[1] –NCCN Guidelines	39	157	45	177	1	0.12	**0.03**
Black (n=60) White/Other (n=218)	(65.00%)	(72.02%)	(75.00%)	(81.19%)			
Had Genetic Testing	2	11	4	18	1[#]	0.68[#]	0.25[#]
Black (n=87) White/Other (n=344)	(2.30%)	(3.20%)	(4.60%)	(5.23%)			

* Intention to Treat

[#] Fischer Exact Test

1. Excludes YBCSs with double mastectomy
2. Excludes relatives younger than 35 years old AND relatives between 35 to 40 with Gail lifetime risk <20% according to NCCN guidelines

Bold= significant difference ≤ 0.05

Satisfaction with the interventions

Approximately 96% of participants reported reading the intervention materials at least once and discussing them primarily with first-degree and with non-biological relatives (**Table 5**), most often females and/or relatives from the maternal side of the family (data not shown). Black participants systematically reported higher satisfaction and acceptability of the interventions, including getting new information that helped them talk with their healthcare providers about lowering their breast cancer risk. Relatives requested more information about breast cancer risk factors, low cost screening, breast cancer genetics and genetic testing, and family communication in breast cancer.

Table 5. Evaluation of the tailored and targeted interventions

I discussed the information in the booklet(s) and letter with…							
No one						324	
Not a biological relative (spouse, in laws, friend)						323	
First degree relatives (mother, father, sister, brother, children)						700	
Second degree relative (grandmother, grandfather, grandchildren, aunts, uncles, nephews, nieces)						163	
First cousins						65	
Healthcare provider (oncologist, genetic specialist, nurse, primary care provider)						124	
Other						5	
The brochures and letter I received… [1-7]	**Overall**	**YBCS**	**Relatives**	**Tailored**	**Targeted**	**Black**	**White/ Other**
…provided me with new information	4.84	4.77	4.94	4.81	4.87	**5.07**	**4.74**
…provided helpful information	5.15	5.16	5.14	5.14	5.17	**5.36**	**5.07**
…were overall easy to understand, important, useful, and interesting*	5.04	5.05	5.04	5.06	5.02	**5.35**	**4.93**
…helped me talk with my healthcare provider about my breast cancer risk	4.26	4.24	4.32	4.28	4.25	**4.74**	**4.07**
…helped me talk with my healthcare provider about ways to lower my cancer risk	4.23	4.21	4.25	4.22	4.23	**4.70**	**4.02**
I would like to get more information about… [1-7]	**Overall**	**YBCS**	**Relatives**	**Tailored**	**Targeted**	**Black**	**White/ Other**
…risk factors for breast cancer	4.87	**4.67**	**5.22**	4.87	4.88	**5.39**	**4.66**
…importance of family history for cancer risk	4.90	**4.71**	**5.22**	4.83	4.98	**5.46**	**4.67**
…genetic counseling and genetic testing	4.83	**4.73**	**5.02**	4.75	4.92	**5.47**	**4.57**
…where to get genetic counseling and testing	4.70	**4.58**	**4.90**	4.67	4.74	**5.39**	**4.41**
…breast cancer screening	4.86	**4.71**	**5.10**	4.86	4.86	**5.43**	**4.63**
…low cost breast cancer screening	4.52	**4.37**	**4.75**	**4.37**	**4.68**	**5.29**	**4.20**
…family communication in breast cancer	4.26	4.18	4.41	**4.13**	**4.41**	**5.04**	**3.95**
…family support in breast cancer	4.22	4.14	4.36	4.11	4.34	**4.98**	**3.91**

I would suggest the study to women like me	5.77	5.81	5.70	5.77	5.77	**6.05**	**5.66**
The study was important	6.16	6.16	6.16	6.22	6.10	**6.37**	**6.08**
I benefited from taking part in the study	5.57	5.51	5.67	5.61	5.53	**5.97**	**5.40**

Bold= significant difference p≤0.05

*average of 16 items

DISCUSSION

An important finding of the RCT was that there was an approximate 10% increase from pre- to post-intervention in reported CBE and mammography rates among YBCS and relatives across both study arms. Findings suggest that the booklet on cancer surveillance and genetic testing, and the personalized letters were an efficient and low-cost strategy for increasing screening, while having minimal contact with participants. Within group differences showed that YBCS and relatives in the tailored arm were more likely to report CBE and mammograms consistent with NCCN guidelines, especially for participants needing less support from healthcare providers. Tailored feedback improves the impact of the message on health behaviors [27,28] because the message addresses participants' personal needs and characteristics[29]. Participants are more likely to pay attention and process the information presented in tailored messages[29]. Tailored interventions report an increase in mammography uptake [30,31]. Given the minimal contact with participants and that 80% of YBCS and 70% of relatives reported high rates of CBE and mammography at baseline, leaving less room for improvement, the outcomes of the RCT are commendable, and indicate that we selected appropriate tailoring targets for health behaviors that need to be repeated over time, such as CBE and mammography screening.

Genetic testing uptake in our RCT was lower than other studies providing genetic information either in person or by telephone [20,21]. At the same time, the tailored intervention provided persuasive and effective messages to YBCS and relatives who reported higher self-efficacy and intention for genetic testing. Thus, the tailored intervention generated an added value, since self-efficacy and intention are important intervention targets among breast cancer survivors. The lower uptake of genetic testing may be related to other factors, including the short term follow-up of eight months, the recruitment strategy precluding a referral from a healthcare provider, and the fact that YBCS were on average 11 years post diagnosis and genetic testing may not have been perceived as

relevant or urgent[32]. Furthermore, relatives' eligibility for genetic testing depends first, on the YBCS having genetic testing as the affected family member, and second, on the YBCS' test identifying a pathogenic variant associated with HBOC. There was no difference in participant satisfaction between the two intervention arms. Since rates of genetic testing at baseline were low and there was little variation among study participants for this key outcome, we will examine in a future study if our targeted booklet yields better rates of genetic testing when integrated in the healthcare system and the message is reinforced by appropriate healthcare provider referrals. Future studies should also examine the cost-effectiveness of tailored interventions for genetic testing [29]. Alternatively, a stepped approach with additional resources (e.g., personal contact) for those who do not respond to the initial invitation may prove efficacious and cost-effective.

This was the first public health intervention that included a large sample of Black YBCS. Within groups comparisons showed that Black participants did not report higher CBE or mammography rates, or higher genetic testing uptake. However, they were significantly more likely to report higher self-efficacy and intention for genetic testing, and higher satisfaction with intervention materials and with their participation in the study. Black participants were also significantly more likely to report needing additional information about breast cancer surveillance and genetic services. Taken together these findings suggest that study materials achieved cultural appropriateness and high acceptability among Black participants, which has been shown to increase intervention efficacy and effectiveness among special populations [33-35]. We explored reasons for underutilization of cancer genetic services among Black YBCS in our sample, and we identified that although they live closer to these services, they report significant lack of physician referrals and higher cost-related lack of access to care [36-38]. Significant social inequalities created by differences in income and education cannot be attributed to cultural differences. Once the financial barriers have been bridged, our intervention materials can be used to empower minority communities and engage them in public health policies regarding genetic screening[39].

A strength of the study is the partnership between a state health department and a leading academic institution, which demonstrated that they can help implement health promotion interventions with families at high risk for hereditary cancers. Despite the larger number of Black participants compared to previous studies, it may still have been underpowered to detect genetic testing outcomes among Black relatives. The intervention was theory-based and measures were reliable and valid, however, outcomes regarding screening behaviors and uptake of genetic testing were based on self-report. A limitation may have been allowing only eight months to observe changes in behavioral outcomes and that information about genetic services was not relevant for a large number of YBCS and relatives not living in Michigan.

METHODS

Design and Sample

This two-arm cluster RCT was conducted in the state of Michigan (NCT01612338) [40]. Institutional Review Boards of the University of Michigan (HUM00055949) and the Michigan Department of Health and Human Services (201202-09-EA) approved the study protocol. A random sample of 3,000 YBCS was selected from approximately 9,000 YBCS registered in the Michigan Cancer Surveillance Program (MCSP). They were stratified by race (1,500 Black and 1,500 White/Other) with oversampling of Black YBCS. Approximately 7% of YBCS of other racial/ethnic backgrounds (e.g., Arab Americans etc.) were grouped with White YBCS, because they could not form a separate stratum. YBCS were eligible to participate if they were 20 to 45 years old when diagnosed with invasive breast cancer or ductal carcinoma in situ; 25 to 64 years old at the time of the study; Michigan residents at the time of diagnosis; able to read English and provide informed consent; and not pregnant, incarcerated, or institutionalized. Female relatives had to be cancer-free and 18 to 64 years old; able to read English and provide informed consent; not pregnant, incarcerated, or institutionalized; and the YBCS would be willing to contact them. In order to alleviate ethical concerns in contacting

relatives without their explicit consent, recruitment materials were mailed to YBCS, who passed them on to relatives. Up to two relatives per YBCS were invited to have comparable family units. Priority was given to younger and first-degree relatives. [25]

Randomization and Masking

The MCSP inquired with the reporting facility and physician of record whether there was any reason that YBCS should not be contacted. If MCSP did not receive a response within 30 days, research staff mailed a recruitment package to YBCS. Eligible YBCS received up to three mailed invitations over a period of 4 months. YBCS who accepted participation were asked in the baseline survey if they were willing to invite their first- and second-degree female relatives in the study. When YBCS reported a hereditary cancer syndrome, research staff contacted them by phone to clarify that the response was not an error and to provide additional information. YBCS and relatives were randomized as stratified (Black vs. White/Other) family units (i.e., dyads and triads) to one of the two study arms (1:1) using a computer-generated allocation algorithm. Participants in both arms received a baseline and a post-intervention survey, and all intervention materials by postal mail. All members of a family unit received intervention materials at the same time and participants were unaware of the materials delivered to the other arm. Participants received $10 gift cards for completing the baseline and $20 gift cards at follow-up survey, respectively.

Data Collection and Measures

Eligible YBCS were mailed a baseline survey (Time 1). Following assessment of their baseline information, their relatives were recruited, and family units were randomized to the targeted or tailored intervention. The follow-up survey (Time 2) was mailed to participants approximately 8 months after the intervention to allow sufficient time for pursuing primary outcomes (CBE, mammography, genetic testing). Participants received two reminders to complete the follow-up

survey. **Table 6** describes the instruments used to assess breast cancer screening and use of genetic testing. The 8-month follow-up survey included questions assessing whether the interventions provided new and helpful information, and examined intervention acceptability, interest, usefulness, level of detail, relevance, and satisfaction (Likert scale 1=low to 7=high)[41,42].

Table 6. Measures used to assess covariates and outcomes

	Instrument	YBCS		Relative	
		Baseline	Follow-up	Baseline	Follow-up
ANTECEDENTS					
Demographics					
• Age, Race, Education	Behavioral risk factors surveillance system[43]	√		√	
• Income, Insurance	Behavioral risk factors surveillance system[43]	√		√	
• Routine source of care	Coordination of medical care (multiple choices)	√		√	
• Cost-related lack of access	High out-of-pocket costs (yes/no)	√	√	√	√
• Distance – genetic services	Great Circle Distance Formula[44]	√		√	
• Caregiving responsibilities	Lives with children under 18 years old and/or with elderly parents	√		√	
Health history					
• Anxiety, Depression, Comorbidities	Anxiety, Depression, and 11 chronic conditions associated with mobility (yes/no)[45]	√	√	√	√
• Cancer and family history	Behavioral risk factors surveillance system (validated)[43]	√	√	√	√
• Surgery	American Society of Clinical Oncology (ASCO) guidelines[4]	√	√		
• Reproductive history	Risk factors associated w/ the Gail and the Claus models[46-48]			√	√
Family characteristics					
• Family Coherence	Family Hardiness Index, 20 items, 7-point Likert scale[49]	√		√	
Facilitators and barriers					
• Barriers for mammography	Decisional balance scale for mammography, 20 items, 7-point Likert scale[50]	√	√	√	√
• Perceived expectations of healthcare providers	1 item, 7-point Likert scale *"Do you believe that your doctor or other healthcare providers want you to get [genetic testing] to find cancer at an early stage?"*	√		√	
BREAST CANCER SURVEILLANCE AND GENETIC TESTING					
• Cancer surveillance (CBE, mammography)	NCCN Guidelines[51]	√	√	√	√
• Genetic services (testing)	NCCN Guidelines[51]	√	√	√	√

• Self-efficacy (CBE, mammography, genetic testing)	1 item, 7-point Likert scale *"During the next 12 months how confident do you feel in your ability to ask your doctor or other healthcare provider for [genetic testing for hereditary cancer]."*	√	√	√	√
• Intention (CBE, mammography, genetic testing)	1 item, 7-point Likert scale *"During the next 12 months how likely are you to ask your doctor or other healthcare provider if [genetic testing for hereditary cancer] is a right test for you."*	√	√	√	√

Statistical Analyses

Descriptive analyses compared means and proportions in demographic and clinical factors (i.e., age, race, education, income, having a routine source of care, caregiving responsibilities, mobility-related comorbidities, anxiety, depression, cost-related lack of access to genetic services, and distance to the closest genetic center) between and within intervention groups across time (baseline and 8-month follow-up). We performed separate analyses for YBCS and relatives for CBE, mammography, and genetic testing. Changes in frequencies were demonstrated after using Intention-To-Treat, and comparisons between and within intervention groups were done with z-tests.

We examined core features of missing data (less than 18%) and dropout cases that did not complete the follow-up survey. No special patterns of missing values were identified. We used demographic variables and/or baseline outcome variables to examine if there is a clear pattern of lost to follow-up across subgroups using machine-learning approaches (logistic regression, Markov Chain Monte Carlo, generalized linear mixed model and quadratic discriminant analysis)[52-54]. Machine-learning approaches indicated random drop out patterns across subgroups, which allowed for multiple imputations to address missing values and dropouts for subsequent analyses. Multiple linear regression models tested associations between intervention effects and co-variables. Co-variables were intervention grouping (tailored versus targeted), demographic and clinical factors.

Sample Size and Power Evaluation

Using data from previous mammography screening interventions[22,55], power analysis with PASS software [56] determined that after attrition 176 participants were needed per group (352 in total). This sampling rate ensures 80% power to detect a medium to small difference in intervention effect size between group means (d=0.3) or between percentages (h=0.3), using a two-tailed test with a false positive rate of α= 0.05.

CONCLUSIONS

In conclusion, this RCT is aligned with evidence-based recommendations for public health action relevant to cancer genetics [57,58]. We addressed all behaviors related to breast cancer surveillance and genetic surveillance according to national recommendation guidelines [3,4]. Adoption of these guidelines will achieve a population-level reduction in cancer morbidity and mortality. The RCT suggests that a combination of targeting and tailoring health communication can be an effective strategy in achieving optimal outcomes and maximizing resources for cancer surveillance and genetic testing [59].

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Author Contributions

Conceptualization, Maria C. Katapodi, Laurel L. Northouse and Sonia A. Duffy; Data curation, Kari E. Mendelsohn-Victor; Formal analysis, Chang Ming and Ivo D. Dinov; Funding acquisition, Maria C. Katapodi, Laurel L. Northouse, Sonia A. Duffy, Debra Duquette and Sofia D. Merajver; Investigation, Maria C. Katapodi and Debra Duquette; Methodology, Maria C. Katapodi and Laurel L. Northouse; Project administration, Debra Duquette and Kari E. Mendelsohn-Victor; Software, Kari E. Mendelsohn-Victor; Supervision, Maria C. Katapodi; Validation, Laurel L. Northouse, Sonia A. Duffy, Debra Duquette, Kara J. Milliron, Sofia D. Merajver and Nancy K. Janz; Writing – original draft, Chang Ming; Writing – review & editing, Maria C. Katapodi, Laurel L. Northouse, Sonia A. Duffy, Kara J. Milliron and Nancy K. Janz.

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