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Impact of self-reported data on the acquisition of multi-generational family history and lifestyle factors among women seen in a high-risk breast screening program: a focus on modifiable risk factors and genetic referral

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Abstract

Background—The phrase “high-risk for breast cancer” is used to identify various groups at elevated cancer risk and the appropriate surveillance and risk-reducing strategies differ based on the etiology of risk. Here we review the utility of patient-reported data to capture women with modifiable lifestyle risk factors and those suitable for genetic counseling referral.

Methods—Patient-reported data from a web-based survey were used to capture personal history, multigenerational family history and lifestyle factors (body mass index, alcohol consumption, physical activity). Responses were tabulated, and percentage of patients who met criteria for possible intervention calculated.

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Results—1277 women completed the survey from 10/2014–12/2015. Women were considered high risk for a combination of the following: family history of breast and/or ovarian cancer (77%), history of atypical hyperplasia or lobular carcinoma in situ (35%), known breast-cancer–related gene mutation (11%). Based on self-reported data, 65% qualified for genetic evaluation but 40% reporting no prior testing. Only half of the population met national physical activity recommendations, nearly 40% were overweight/obese, and 18% reported consuming 1 alcoholic beverage per day.

Conclusions—Among women followed in a high-risk breast surveillance program, there is considerable opportunity for improved genetic referral and awareness of modifiable lifestyle factors based on self-reported data as 60% of respondents reported a possible area for intervention. While risk reduction associated with lifestyle changes is modest in comparison to chemoprevention or surgery, such changes are practically without risk, minimally expensive, and provide innumerable secondary health benefits.

Keywords

breast cancer risk; genetic testing; lifestyle; health behavior

Introduction

Women may be considered high-risk for breast cancer development secondary to both familial and personal risk factors, with wide variation in level of risk attributable to different risk factors. Identification of women at risk for genetic predisposition to breast cancer is important, as studies have shown improved outcomes among BRCA carriers undergoing increased surveillance or risk-reducing surgery [1,2]. While a minority of women with a family history of breast cancer have a deleterious mutation, identification of these mutations in the non-affected individual allows for appropriate counseling and opportunities for risk reduction.

Within a high-risk breast surveillance program, most women are considered to be at elevated risk secondary to a high-risk breast lesion (atypical hyperplasia or lobular carcinoma in situ [LCIS]) or family history without an identifiable gene mutation, and have generally been offered chemoprevention for risk reduction. Chemoprevention with a selective estrogen receptor (ER) modulator or an aromatase inhibitor has been shown to reduce the risk of ER positive breast cancer in women at increased risk by roughly 50%, but may be accompanied by menopausal symptoms, increased risk of endometrial cancer, arthralgias, and thromboembolic events [3–7]. Despite robust evidence supporting the benefit of chemoprevention, an overwhelming majority of eligible women opt not to take chemoprevention, citing fear of side effects and a perception of being low risk [8,9]. Given the aversion to pharmacologic risk reduction, lifestyle modifications provide an alternative, non-toxic mechanism for possible risk reduction. Modifiable lifestyle factors associated with breast cancer risk include obesity, alcohol consumption, and physical inactivity (Table 1) [10–21].

The aim of this study was to identify the ability of patient reported data to identify women within a large high-risk breast surveillance program with risk factors suitable for

intervention, including family history suggestive of a breast cancer genetic syndrome or modifiable lifestyle factors.

Methods

Women seen in the Memorial Sloan Kettering Cancer Center Risk Assessment, Imaging, Surveillance, and Education (RISE) program from October 2014 through December 2015 who completed a web-based survey (RISE-Webcore) prior to their appointment were identified. The survey was designed for women new to this program, but at the time of initial survey unveiling, all current program participants were invited to complete the survey. Subjects were excluded if they were male ($n = 9$) or had a personal history of invasive breast cancer or ductal carcinoma in situ ($n = 106$).

RISE-Webcore responses were collected from the following survey sections: demographics, lifestyle (body mass index [BMI], physical activity level, alcohol intake, and smoking history), use of endocrine therapy, prior testing for genetic mutations, and personal and/or family history of cancer. The survey includes a detailed family history section, including cancer type and age at diagnosis in first- and second-degree relatives as well as cousins. Using a binomial confidence interval, we estimated the percentage of women in this population who reported not receiving testing for BRCA genetic mutations but who would be recommended to undergo genetic counseling according to their responses on survey items corresponding to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 1.2016 [22] which mirror the updated Version 1.2017 recommendations [23]. There are limitations in applying the obtained results to the NCCN criteria, including absence of information on prostate cancer Gleason score, age of diagnosis by decade, multiple breast cancers in a single relative, lack of gender for breast cancer history in cousins, and omission of information regarding manifestations of Cowden's or Peutz-Jeghers syndrome. We compared the overall results when including prostate cancer versus excluding prostate cancer, and a clinically significant difference was not noted.

The number of women who meet the United States Department of Health and Human Services and American Cancer Society recommendations for exercise (150 minutes of moderate-intensity activity or 75 minutes of vigorous activity a week) was determined [24]. Survey participants were asked to respond with the number of times per week and average duration in minutes for each of the following exercise categories: mild ("minimal effort, no perspiration"; "e.g., easy walking, yoga, golf"), moderate ("not exhausting, light perspiration"; "e.g., fast walking, tennis, easy bicycling, easy swimming"), and strenuous ("heart beats rapidly, sweating"; "e.g., running, aerobics classes, vigorous swimming or bicycling). Our review of this existing clinical data was approved for exemption from IRB/PB Review (WA0395-15). All calculations were done using Stata Version 13 (College Station, TX).

Results

In total, 4491 surveys were assigned; 1392 (31%) were completed. Of the 383 women who had a new visit in the RISE program during the 15 month study period, 244 (64%) completed the survey, 230 of whom met study eligibility criteria. An additional 1047 women in ongoing surveillance in the RISE program completed the survey and met study criteria. Responses from the 1277 eligible participants are summarized in Tables 2–4. The median age of the population was 53 years (range 20–82 years), 214 reported a personal history of prior non-breast cancer and the majority self-identified as White (86%). Nearly one-third reported Ashkenazi Jewish heritage (29%). The majority (77%) had a family history of breast and/or ovarian cancer, 30% reported prior genetic testing, with 11% reporting a deleterious gene mutation. 489 women (35%) reported a history of a high-risk breast lesion (LCIS, atypical hyperplasia)(Table 2).

Based on responses to the family/personal history and demographic items, 65% (95% confidence interval [CI] 62–67%) of survey respondents qualify for genetic evaluation using the 2016 NCCN criteria, while 40% of this group (95% CI 38–43%) reported no prior BRCA testing (33% of women seen as a new visit, 42% of those in follow-up). The most common patient qualification for genetic testing was family history of 3 relevant cancers (51%), followed by having a close relative diagnosed with ovarian cancer (18%) or more than one close relative diagnosed with breast cancer prior to 40 years of age (17%)(Table 3). Among 433 women previously seen in the RISE program who reported a family history suggestive of a genetic syndrome without prior genetic testing, 312 (72%) had a documented discussion regarding genetic evaluation and either were recommended to undergo testing and declined or were not referred for testing secondary to affected family members' testing negative.

In our analysis, we also observed opportunities for improved advocacy on physical activity initiatives, as only 50% (95% CI 47%, 54%) of respondents met the recommendation for weekly activity level by reporting either 150 minutes of moderate exercise or 75 minutes of vigorous exercise per week. In addition, more than one-third (38%) self-reported as being either obese (14%) or overweight (24%). Current use of cigarettes was low (2.8%), with 375 women (30%) reporting prior tobacco use (no tobacco use within the past 30 days). While 251 (20%) women reported never drinking alcohol, 228 (18%) reported having 1 alcoholic beverages per day (Table 4). Only a small fraction reported having used endocrine therapy, with 5.2% reporting having ever used tamoxifen and 4.0% reported having ever used raloxifene (no patients reported exemestane use).

Discussion

Breast cancer risk assessment and stratification is important to allow personalized screening recommendations and risk-reducing strategies. Among a cohort of over 1000 high-risk women who self-reported breast cancer risk factors, 60% indicated an opportunity for outreach in either education on lifestyle factors or referral for genetic counseling. While it is not surprising that 33% of women new to the high-risk program met genetic referral criteria but had no prior testing, patient-reported data identified a small cohort of women (n = 121)

in ongoing follow-up who meet the 2016 NCCN genetic referral guidelines without prior genetic testing recommendations, highlighting the importance of updating family history for ongoing risk assessment in accordance with changing genetic referral guidelines. In a similar review comparing an electronic, computer-based, patient-reported family history versus physician-obtained family history [25] in an ambulatory cancer center clinic, 101 patients were assigned to a high-risk category by self-reported family history, but only 14% were classified as such by the physician, and only 7% were referred for genetic consultation. Patient-reported data on family history can provide detailed information that may be omitted during a focused clinic visit and provide an efficient method of data collection to aid in risk stratification. Identification of a deleterious mutation is important in personalizing breast cancer screening and risk-reduction recommendations. Enhanced screening of BRCA mutation carriers with MRI has been shown to identify smaller, earlier-stage tumors [26,27]. In addition, many women with a known deleterious mutation opt for risk reduction with bilateral prophylactic mastectomies [2,28] which is associated with a greater than 90% reduction in breast cancer risk [29]. For these reasons, appropriate referral for genetic counseling and testing has the potential to substantially alter management.

While a minority of women in this high-risk sample have a deleterious mutation, all met criteria for chemoprevention for risk reduction based on elevated lifetime breast cancer risk, yet < 10% reported a prior or current use of chemoprevention. Similar to other reports [30], uptake of chemoprevention among high-risk women remains poor, emphasizing the need for additional non-toxic risk-reducing strategies. Using patient-reported responses to lifestyle factors, we identified areas for improved patient awareness and lifestyle changes, including alcohol consumption, obesity, and physical activity.

Alcohol

Alcoholic beverages are causally related to the development of numerous cancers, and the World Health Organization added female breast cancer to that list in 2007 [31]. The first study revealing this association was published in 1977, followed by a plethora of epidemiologic reports and meta-analyses [32]. Singletary and Gapstur published a comprehensive review of > 40 epidemiologic studies evaluating the association of alcohol consumption and risk of breast cancer, with most studies finding a relative risk between 1.5 and 2.0 [20]. Multiple large pooled analyses conclude the relative risk increases steadily with increased alcohol intake, rising 7–9% for each additional 10-gram increment of alcohol intake, which was not modified by additional factors [15,33]. The dose-dependent, linear association between alcohol consumption and increased breast cancer risk for both premenopausal and postmenopausal women is thought to occur at levels as low as 1–2 drinks per day.

The alcohol intake quantified in our study indicates that nearly 20% of patients consume at least 1 drink every day. One large study revealed daily consumption of 50 grams of alcohol, roughly 3.5 drinks, was associated with a 50% increase in risk of breast cancer when compared to non-drinkers [15]. In regions of the United States, or in other countries such as Italy, where the average intake is significantly higher than in the U.S., the proportion of breast cancer cases that are thought to be attributed to alcohol is over 10% [15,34,33]. In the

United States, two-thirds of the adult population are classified as current drinkers; 29.5% as light drinkers (average 3 drinks/week), 8.6% as moderate (3–7 drinks/week), and 4.8% as heavy (7+ drinks/week) [35]. Using these Centers for Disease Control and Prevention (CDC) definitions, our population is comprised of nearly 20% of women classified as heavy drinkers, identifying a population who warrant education regarding the relationship between alcohol consumption and breast cancer risk.

Obesity

Postmenopausal obesity has been associated with an increased risk of breast cancer in a number of large epidemiologic studies [36,37,21]. Pooled analyses from 7 major prospective cohort studies found a positive association between elevated BMI and increased breast cancer risk in postmenopausal women [21]. The relative risk associated with a moderately overweight BMI (25–29.9 kg/m²) from this study was 1.26, replicated in a second large meta-analysis at 1.25 for women with a BMI ≥ 30 kg/m² [36,21]. Using European body mass prevalence data, it was estimated that the excess risk for overweight and obese postmenopausal women is 12% and 25%, respectively, resulting in a total of 12,800 attributable excess breast cancer cases annually in Europe [36].

Consistent with national trends, a large proportion of women (40%) in our high-risk surveillance program meet CDC definitions of being overweight or obese. Of these, 24% were classified as overweight and 14% as obese, as compared to the national average of 28.2%, and 27.2%, respectively [35]. Our results highlight a significant potential benefit for diet modification, weight loss, and exercise enrichment in a high-risk breast clinic.

Activity Level

Physical activity has been shown to markedly reduce breast cancer risk, with an approximate 25% average risk reduction for women who regularly participate in physical activity when compared to the least-active women [14]. One study found women who regularly exercised roughly 4 hours or more per week had less than half the odds of breast cancer compared to inactive women (odds ratio 0.42, 95% CI 0.27–0.64) [11]. This protective effect appears to be stronger when exercise is performed throughout one's lifetime or performed after menopause, is regular, and is of moderate to strenuous intensity. The mechanism by which exercise exerts its effects are likely multifactorial, and may be related to degree of adiposity, total BMI, relative estrogen levels, insulin sensitivity, and chronic inflammation [14].

Only 50% of survey respondents meet national standards for exercise as defined by the United States Department of Health and Human Services and the American Cancer Society [24], which recommend 150 minutes of moderate-intensity activity or 75 minutes of vigorous activity a week. Based on these results, education regarding the association between exercise and breast cancer risk may benefit a large cohort of women at high risk and support ongoing research initiatives that address the impact of exercise on breast cancer risk reduction.

The increased relative risks of breast cancer associated with lifestyle factors are modest and comparable to women who have proliferative lesions without atypia (RR 1.7–1.9) [13,16] and those with a first-degree relative with breast cancer (RR 1.8–2.1) [12,18]. However,

these are areas that women may modify independently, simply, and with minimal risk. High-risk breast clinics are ideal forums for identification of modifiable risk factors for breast cancer, education, advocacy, and referral when appropriate.

Strengths of this study include the large dataset of patient-reported information from a population of nearly 1300 unaffected high-risk women seen in a breast surveillance program. This study is limited because of the self-selection of women who choose to respond to the survey, and, therefore, the results do not represent the entire high-risk cohort. The RISE program is somewhat regionally specific in light of a high Ashkenazi Jewish population, and lower rates of smoking and obesity than national statistics indicate, and therefore may not be representative of all women. In addition, we acknowledge that not all women counseled to lose weight, decrease alcohol consumption, or increase physical activity will adhere to those recommendations. However, identifying women with modifiable risk factors and providing risk-reducing strategies allows motivated women to change. Here we see that a substantial proportion of women concerned enough about their breast cancer risk to attend a high-risk breast surveillance program have modifiable risk factors and indications for genetics referral. A web-based survey is an efficient method to collect such information. Our response rate among new visits was high, indicating that the web-based survey is a viable method of data collection. The lower response rate among those already in the surveillance program may in part reflect that women in follow-up have previously provided some of this information as part of their care and did not feel that it was necessary to respond.

Conclusion

A substantial number of women seen in a high-risk breast surveillance program report areas for potential intervention, including genetic evaluation for a hereditary breast cancer syndrome as well as education regarding the role of modifiable lifestyle factors on breast cancer risk, highlighting the benefit of patient-reported data to gather detailed information that may personalize genetic referral or risk-reducing strategies. While overall risk reduction from lifestyle modifications is modest in comparison to chemoprevention or surgical risk reduction, the interventions are practically without risk, minimally expensive, and provide innumerable secondary health benefits to women, while reducing breast cancer risk.

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Table 1

Risk factors for breast cancer.

Factor	Relative Risk Breast Cancer
BRCA mutation [10]	10–33 *
Chest wall radiation (age < 30) [17]	8.2
Proliferative lesions with atypia (ADH/ALH) [13,16]	3.9–4.2
Multiple first degree relatives with breast cancer [12,18]	2.9–3.9
Single first degree relative with breast cancer [12,18]	1.8–2.1
Proliferative lesions without atypia [13,16]	1.7–1.9
Alcohol consumption [15,19,20]	1.5–2.0
Obesity [21]	1.25
Physical activity [11,14]	0.42–0.75

* Relative risk differs between BRCA1 and BRCA2 as well as age cohort

ADH atypical ductal hyperplasia, *ALH* atypical lobular hyperplasia

Table 2

Patient-reported demographics.

Patient-Reported Demographics	N = 1277
Age at visit, years (range) *	53 (44, 61)
Race (n = 1271)	
White	1095 (86%)
Asian	61 (4.8%)
Hispanic or Latino	50 (3.9%)
Black or African American	37 (2.9%)
Other	24 (1.9%)
Pacific Islander	4 (0.3%)
Ashkenazi Jewish heritage (n = 1254)	
No	853 (68%)
Yes	365 (29%)
Don't know	36 (2.9%)
Reason for visit	
History of breast atypia	333 (26%)
History of LCIS	156 (12%)
Radiation treatment to chest area	22 (1.7%)
Family history of breast and/or ovarian cancer	977 (77%)
Gene mutation or syndrome that increases breast cancer risk [‡]	137 (11%)
None of the above but interested in finding out breast cancer risk	54 (4.2%)
No reason selected	21 (1.6%)

* All values are: Median(Interquartile Range) or n (%) unless otherwise specified

[‡] Mutations include: n = 59 BRCA1, n = 73 BRCA2, n = 1 Li-Fraumeni Syndrome (p53), n = 1 Cowden syndrome (PTEN), n = 1 hereditary diffuse gastric cancer syndrome (CDH1/E-cadherin), n = 2 CHEK2, n = 1 PALB2, no patients selected mutation options: Ataxia Telangiectasia Mutated (ATM), Peutz-Jeghers Syndrome (STIKII), Muir-Torre Syndrome (MSH2), or BRCA1 Interacting Protein (BRIP). Seven women reported 2 mutations, 3 reported "other", and 3 did not make a selection.

LCIS lobular carcinoma in situ

Table 3

Patient-reported data meeting national comprehensive cancer network criteria for genetic assessment among women with and without prior genetic testing.

NCCN Criteria for Genetic Assessment	Overall Meeting NCCN Criteria 825/1277 (65%)	Meets NCCN Criteria without prior testing 509/1265 (40%)
	n = 1277	n = 509
Ashkenazi Jewish with personal history of ovarian or pancreatic cancer	23 (1.8%)	2 (0.4%)
Personal history of ovarian cancer	44 (3.4%)	3 (0.6%)
3 or more instances of close [†] family members diagnosed with cancer ^{††}	646 (51%)	422 (83%)
3 or more instances of a personal history of cancer ^{††} or close [†] family members diagnosed with cancer ^{††}	663 (52%)	435 (85%)
More than one close [†] relative on same side of family diagnosed with breast cancer, with at least one diagnosed prior to age 50	51 (4.0%)	28 (5.5%)
Close [†] relative diagnosed with ovarian cancer	231 (18%)	105 (21%)
Close [†] relative diagnosed with a male breast cancer	25 (2.0%)	11 (2.2%)
First- or second-degree relative diagnosed with breast cancer prior to age 40	214 (17%)	124 (24%)

* All values are: n (%) unless otherwise specified

[†] Excludes breast cancer

^{††} List of relevant cancers covered by the RISE-Webcore survey: breast, pancreatic, melanoma, sarcoma, adrenal, brain, leukemia, stomach, rectal, thyroid, kidney, prostate, and endometrial/uterine

[‡] Close relative encompasses the first-, second-, and third-degree relatives covered by the RISE-Webcore survey

NCCN National Comprehensive Cancer Network, CI confidence interval

Table 4

Patient-reported data regarding modifiable lifestyle factors.

Lifestyle Factor	N* 1277
Alcohol Use: Typical number of alcoholic drinks per week (n=1267)	
Never	251 (20%)
< 1 drink/week	421 (33%)
1–2 drinks/week	367 (29%)
1 drink/day	177 (14%)
2–3 drinks/day	49 (3.9%)
4 drinks/day	2 (0.2%)
BMI[†] (n=1192)	
Underweight (< 18.5)	44 (3.7%)
Normal/healthy weight (18.5 to 24.9)	691 (58%)
Overweight (25.0 to 29.9)	285 (24%)
Obese (≥ 30.0)	172 (14%)
Physical Activity: Total minutes of exercise per week^{**} (n=881)	
Mild exercise (n = 638) ^{††}	80 (30, 140)
Moderate exercise (n = 689) ^{††}	60 (0, 135)
Vigorous exercise (n = 705) ^{††}	45 (0, 135)
	Proportion (95% CI)
Meets exercise guidelines[‡] (n = 830)	50% (47%, 54%)

* All values are: Median (Interquartile Range) or n (%) unless otherwise specified

[†]BMI (Body Mass Index, as defined by the Centers for Disease Control and Prevention, kg/m²)

^{††}Mild (minimal effort, no perspiration), Moderate (not exhausting, light perspiration), Vigorous (heart beats rapidly, sweating)

[‡]At least 150 minutes of moderate activity or 75 minutes of vigorous activity per week, as defined by the U.S. Department of Health and Human Services and the American Cancer Society

^{**}Exercise questions only made available to patients taking a more recent version of the questionnaire (n = 881).