Research Article

Breast Cancer Chemoprevention in Primary Care- Assessing Readiness for Change

Haiyun Wang
Gesinger Health System, Danville, PA, USA

Claire F Snyder
Johns Hopkins University School of Medicine, Baltimore, MD, USA

Sharon Larson
Gesinger Health System, Danville, PA, USA

Victor Vogel
Gesinger Health System, Danville, PA, USA

H Lester Kirchner
Gesinger Health System, Danville, PA, USA

Haiyan Sun
Gesinger Health System, Danville, PA, USA

Xiaowei Yan
Sutter Health System, San Francisco, CA, USA

ABSTRACT

Purpose: Despite breast cancer chemoprevention recommendations, chemoprevention use remains low. We assess primary care providers' (PCP) awareness and use of breast cancer chemoprevention, and perceived barriers/ solutions.

Methods: We conducted an online survey to investigate PCPs' awareness and use of breast cancer chemoprevention, and perceived barriers/solutions. 161/426 (38%) eligible PCPs completed the survey.

Results: Of providers, 42% reported using breast cancer risk assessment models, only 9% prescribed breast cancer chemoprevention drugs in the past year. Providers using risk models were more likely to have made a breast cancer diagnosis in the past year (77% *vs.* 56%; p=0.01). Providers prescribed chemoprevention were older (mean 49 years *vs.* 40; p=0.01), more likely to be in practice ≥ 10 years (71% *vs.* 43%; p=0.04) and full time (79% *vs.* 49%; P=0.04); they all had diagnosed breast cancer in the past year (100% *vs.* 61%;

p=0.002). Top three reported barriers to chemoprevention guideline adherence were lack of knowledge about chemoprevention drugs, unaware of chemoprevention guidelines, and inability to identify high-risk women. After adjustment for other provider characteristics and barriers, the PCPs who are unaware of chemoprevention guidelines have 3.1 increased odds (CI: 1.4-6.7) for not using risk assessment models. If high-risk women can be identified, 85% of respondents prefer referring appropriate women to a high-risk breast clinic.

Conclusion: PCPs infrequently assess breast cancer risk and rarely prescribe chemoprevention drugs for risk reduction. PCP education on breast cancer prevention and establishing high-risk breast clinics may improve breast cancer chemoprevention uptake.

Keywords: Breast cancer; Risk assessment; Chemoprevention; Guidelines; Primary care

Introduction

Breast cancer is the second leading cause of cancer death in women; about one in eight American women will develop breast cancer in her lifetime.[1] Primary prevention has an important role in decreasing breast cancer incidence, yet evidence suggests it is underutilized.[2-4]

The Breast Cancer Prevention Trial (BCPT) demonstrated a striking 49% reduction in the risk of invasive breast cancer among high-risk women (Gail 2 model 5 year breast cancer risk >1.66%) who took tamoxifen for 5 years.[5-7] The Raloxifene use

for the Heart (RUTH) trial demonstrated raloxifene reduced risk of breast cancer by 44% in postmenopausal women who were at high risk of breast cancer.[8] Evidence-based clinical guidelines exist for the use of chemoprevention in reducing the risk of breast cancer in high-risk women. Both the American Society of Clinical Oncology (ASCO) and US Preventive Services Task Force (USPSTF) recommend these two drugs for breast cancer risk reduction among high-risk women, with the guidelines updated and reinforced in 2013.[9-11]

Although study showed large population of white US women would benefit from breast cancer chemoprevention, most of this

high-risk population does not receive chemoprevention.[2-4,12] A recent study indicates there is no increase in the overall chemoprevention uptake from 2000 to 2010.[4] Primary care providers (PCP) are particularly important for chemoprevention as most high-risk women are seen in primary care. Yet only 10-30% of primary care physicians reported ever having prescribed tamoxifen or raloxifene for breast cancer prevention in the past year.[13-15]

Improving PCP awareness of breast cancer chemoprevention has the potential to benefit a large population of women. Our objective was to investigate the current practice of breast cancer risk assessment and chemoprevention and assess barriers to guideline uptake, in a rural health care system. We also investigated potential solutions to overcome barriers and promote guideline adherence for breast cancer chemoprevention.

Methods

Sample selection and survey procedures

We surveyed all eligible primary care providers in the Geisinger Health System (GHS). Inclusion criteria for this study were as follows: family physicians or internists, physician assistants, and nurse practitioners providing continuous medical care in a family, internal medicine or OB-GYN outpatient clinic for at least a half day per week. The survey was sent to providers' institute email address. The institutional review board of the GHS approved this study.

The online survey was conducted from September to October 2015 using the Qualtrics software platform. Study participants received a recruitment email one week before the survey. Then we sent out the survey email to each study participant with a cover letter and a link to take the survey. The cover letter explained the purpose of the survey. Completion of the electronic survey questionnaire served as consent to participate in the study.

We implemented four strategies to increase the survey response rate: (1) chance to win one of three iPad minis from a drawing of completers (explained in survey cover letter); (2) survey advertisement on Our Geisinger Infoweb two weeks before the survey through the end of data collection; (3) email to secretaries and operation managers of all clinics explaining the survey and requesting their assistance in promoting provider completion; and (4) use of Dillman's Total Design Method (TDM)[16] to promote survey response rate by multiple attempts. Specifically, providers who had not completed the survey questionnaire within 1 week received a reminder email containing the survey link and cover letter. The same reminder email was sent to non-responders 3 days later, up to a total of 3 reminder emails.

Survey instrument

The self-administered online questionnaire required approximately 5 minutes to complete and contained no identifying information. The questionnaire was developed based on literature reviews and experience in clinical practice.[14] Prior to the study, the questionnaire was reviewed and pre-tested among five hospitalists and five PCPs (who were excluded from the final survey). The questionnaire was then revised accordingly.

The content of the instrument has three sections:

Section 1 focused on assessing breast cancer risk assessment and chemoprevention utilization in clinical practice. In this section, providers were asked if they ever used breast cancer risk assessment models, and how many times they had prescribed tamoxifen and/or raloxifene for breast cancer chemoprevention within the past 12 months (never, 1 to 4, 5 to 10, more than 10 times).

Section 2 focused on assessing barriers and solutions to applying breast cancer chemoprevention guidelines in primary care. The eight barriers addressed: unable to identify high-risk women, lack of knowledge about chemoprevention drugs, unaware of chemoprevention guidelines, clinical time constraints, lack of reimbursement, very few high-risk patients in the clinic, medication side effects, and concerned about patients' resistance to chemoprevention (assuming patient may be very likely to resist chemoprevention medication). These barriers were based on previous research investigating non-adherence to clinical practice guidelines.[13,14,17,18] In terms of solutions to promote chemoprevention utilization, three possibilities were evaluated: 1) automatically identifying high-risk women through the EHR and displaying it in the clinic chart; 2) referring high-risk women to a high-risk breast clinic; and 3) arranging high-risk women group visits at primary care clinics to encourage chemoprevention uptake. A Likert-type scale (strongly agree, agree, neutral, disagree, strongly disagree) was used to assess provider's preference.

Section 3 was about demographic, professional and clinical practice characteristics, such as gender, year of graduation, specialty (family medicine, internal medicine), title (MD, DO, CRNP, PA-C), type of practice, female patients seen per week, breast cancer cases diagnosed per year and family history of breast cancer.

Statistical analyses

All analyses were based on providers who completed the survey. We summarized participating providers' characteristics overall and by gender and provider type. We also compared the provider characteristics with survey non-respondents.

We identified providers' characteristics associated with breast cancer risk assessment and use of chemoprevention using Pearson's Chi-square tests or Fisher's exact test. The association between breast cancer risk assessment and chemoprevention prescription experience was also assessed.

We calculated the percentage of respondents who answered "agree" or "strongly agree" to each barrier and solution question, and ranked the barriers or solutions by the value of the percentage. To further assess associations between clinical practice characteristics and barriers, we ran a stratified analysis (providers using risk assessment tools or not), followed by a multiple logistic regression model with the statistically significant variables from the stratified analysis included. The variables included in that model were provider's specialty, years of practice, experience of making breast cancer diagnosis, along with two barrier variables "do not know guideline" and "lack of reimbursement".

Subgroup analyses were performed comparing resident and attending physicians' breast cancer risk assessment and chemoprevention practices. All analyses were performed using SAS (SAS v9.4, SAS Institute Inc., Cary, NC).

Results

Out of 426 eligible providers, 161 (38%) completed the online survey. Comparison of respondents and non-respondents showed a significant difference by gender, with males 41% of respondents *vs.* 52% of non-respondents (P=0.03). Attending physicians were less likely to participate in the survey (45% in respondents *vs.* 64% in non-respondents) (P=0.002).

Among respondents, 71% were MD/DOs, 16% physician assistants, and 13% nurse practitioners. The mean age was 41 years, 32% reported a family history of breast cancer. The rest of provider characteristics were listed in Table 1.

Sixty-eight providers (42%) reported having used risk assessment models to assess breast cancer risk in their practice in the past 12 months (Table 2). Providers with experience using risk assessment models were more likely to have made a breast cancer diagnosis in the past year (77% *vs.* 56%; p=0.01). Other provider characteristics, such as gender, years in practice, age, specialty, professional credential and family history of breast cancer, were not associated with breast cancer risk assessment in practice. Only 14 providers (9%) reported having prescribed Tamoxifen or Raloxifene for breast cancer prevention in the past 12 months (Table 3). Providers who ever prescribed chemoprevention were older (49 years *vs.* 40 years, p=0.01) and were more likely to have been in practice ≥ 10 years (71%

Table 1: Characteristics of survey respondents: Overall, by sex and by provider type.

Variables	Overall (n=161)	Provider Sex		Provider Type	
		Female (n=97)	Male (n=64)	MD/DO (n=107)	PAC/CRNP (n=44)
Gender (male)	64 (42.1%)			59 (55.1%)	5 (11.4%)
Years of practice: 10+	69 (45.4%)	36 (40.9%)	33 (51.6%)	45 (42.1%)	24 (54.6%)
Age: Mean (std)	40.7 (12.2)	38.8 (11.6)	43.2 (12.6)	40.6 (12.0)	41.0 (12.8)
Specialty: Family Medicine	72 (48.0%)	42 (48.3%)	30 (47.6%)	42 (39.6%)	29 (67.4%)
Internal Medicine	54 (36.0%)	27 (31.0%)	27 (42.9%)	53 (50.0%)	1 (2.3%)
OB/GYN	24 (16.0%)	18 (20.7%)	6 (9.5%)	11 (10.4%)	13 (30.2%)
Professional credential: MD/DO	107 (70.9%)	48 (55.2%)	59 (92.2%)		
CRNP/PA-C	44 (29.1%)	39 (44.8%)	5 (7.8%)		
Full-time:	78 (51.3%)	45 (51.1%)	33 (51.6%)	43 (40.2%)	34 (77.3%)
***Breast Cancer diagnosis:**	98 (64.5%)	56 (63.6%)	42 (65.6%)	61 (57.0%)	37 (84.1%)
Family hx of breast ca:	49 (32.2%)	29 (33.0%)	20 (31.3%)	30 (28.0%)	19 (43.2%)

*Breast cancer diagnosed by provider in the last 12 months

Table 2: Association of provider characteristics with breast cancer risk assessment.

Physician Characteristic	Risk assessment		P-value
	Never (n=91)	Ever (n=68)	
Age: Mean (std)	39.60 (11.56)	42.27 (12.95)	0.19
***Breast Cancer diagnosis**:	49 (56.32%)	49 (76.56%)	0.01
Years of practice: 10+	37 (42.53%)	32 (50.00%)	0.36
Full time:	43 (49.43%)	35 (54.69%)	0.52
Gender (male):	38 (43.68%)	25 (39.06%)	0.57
Medical training received: USA	70 (81.40%)	54 (84.38%)	0.63
Other country	16 (18.60%)	10 (15.63%)	
Specialty: Family medicine	39 (45.88%)	33 (51.56%)	0.08
Internal medicine	36 (42.35%)	17 (26.56%)	
OB/GYN	10 (11.76%)	14 (21.88%)	
Professional credential: MD/DO	64 (74.42%)	42 (65.63%)	0.24
CRNP/PA-C	22 (25.58%)	22 (34.38%)	
Family hx of breast ca:	29 (33.33%)	20 (31.25%)	0.79
Female patients over age of 35 seen in average week: 0-10	24 (27.59%)	11 (17.19%)	0.23
11-50	42 (48.28%)	39 (60.94%)	
Great than 50	21 (24.14%)	14 (21.88%)	

*Breast cancer diagnosed by provider in the last 12 months

Table 3: Association of provider characteristics with breast cancer chemoprevention.

Physician Characteristic	Used Tamoxifen or Raloxifene for breast cancer prevention		P-value
	Never (n=145)	Ever (n=14)	
Age: Mean(std)	39.92 (12.21)	48.64 (9.12)	0.01
*Breast cancer diagnosis:	84 (61.31%)	14 (100.0%)	0.002
Years of practice: 10+	59 (43.07%)	10 (71.43%)	0.04
Full-time:	67 (48.91%)	11 (78.57%)	0.04
Gender (Male)	57 (41.61%)	6 (42.86%)	0.93
Medical training received: USA	114 (83.82%)	10 (71.43%)	0.27
Other country	22 (16.18%)	4 (28.57%)	
Specialty: Family medicine	64 (47.41%)	8 (57.14%)	0.45
Internal medicine	50 (37.04%)	3 (21.43%)	
OB/GYN	21 (15.56%)	3 (21.43%)	
Professional credential: MD/DO	95 (69.85%)	11 (78.57%)	0.76
CRNP/PA-C	41 (30.15%)	3 (21.43%)	
Family hx of breast ca:	46 (33.58%)	3 (21.43%)	0.55
Female patients over age of 35 seen in average week: 0-10	35 (25.55%)	0	0.06
11-50	72 (52.55%)	9 (64.29%)	
Great than 50	30 (21.90%)	5 (35.71%)	

*Breast cancer diagnosed by provider in the last 12 months

Table 4: Risk assessment & chemoprevention practice: Resident *vs.* attending.

Variables / Physician type	Risk Assessment (Ever)	Chemoprevention (Ever)
Resident physician (41)	16 (39%)	0 (0%)
Attending physician (69)	30 (43%)	11 (16%)
P-value	0.645	0.006

vs. 43%; P=0.04) than non-prescribers. Prescribers also were more likely to practice full-time (79% *vs.* 49%; P=0.04), and all of them had diagnosed breast cancer in the past year (100% *vs.* 61%; p=0.002). There was a clear association between experience of breast cancer risk assessment and risk reduction practice. Providers who had chemoprevention prescription experience were more likely to use risk assessment models (79% *vs.* 39%, p=0.005).

The top three barriers to adopting breast cancer chemoprevention guidelines in primary care reported were lack of knowledge about chemoprevention drugs (76%), unaware of chemoprevention guidelines (66%), and inability to identify high-risk women (61%). Less than half (46%) of providers perceived time constraints as a barrier. After adjusting for providers' characteristics and barriers, providers who were "unaware of chemoprevention guidelines" had more than 3 times the odds of not using a risk assessment tool in practice (OR=3.1, 95% CI: 1.4-6.7, P=0.004).

Regarding solutions to improve breast cancer chemoprevention in primary care, the majority of PCPs (85%) prefer a high-risk breast clinic. Even if risk assessment tools were available in EHR systems to facilitate identification of high-risk women, only 48% of providers chose to provide breast cancer chemoprevention care themselves.

Subgroup analyses comparing resident (N=41) and attending (N=69) physicians' breast cancer prevention practices showed attending physicians had more experience prescribing tamoxifen or raloxifene than resident physicians (16% *vs.* 0%; P=0.006) (Table 4).

Conclusion

Significant advances in a breast cancer risk reduction research over the past decade have offered women several options to reduce breast cancer risk and perhaps to prevent breast cancer. The spectrum of choices varies from lifestyle modification[19-21] to prophylactic use of selective estrogen response modifiers (SERMs)[6-8,22-24] to mastectomy or oophorectomy.[25-27]

Evidence showed prophylactically using SERMs for 5 years can reduce the risk of breast cancer by almost 50% among high-risk women,[6-8,22-24] yet these medications remained underutilized for the purpose of breast cancer prevention. After enhancement of chemoprevention recommendation from ASCO and the USPSTF in 2013, PCPs' perception and practice of breast cancer chemoprevention is still unknown. To our knowledge, this is the first online PCP survey regarding breast cancer risk assessment and chemoprevention with tamoxifen and raloxifene since 2013.

Our study showed 42% of PCPs reported using models for breast cancer risk assessment, but only 9% reported prescribing tamoxifen or raloxifene for breast cancer prevention in the past 12 months. The endorsement of calculating risk using models (such as the Gail model) is higher in this group of

providers compared to other studies;[13] however, the overall chemoprevention prescription rate is lower than the national level of 10-30%.[4,13-15] Because this is the first study of physician-reported SERMs use at the GHS, we do not know the extent to which practice has changed at GHS over the past decade. Our health system's EHR revealed only 4% of high-risk women (Gail model 5 year breast cancer risk of 2+) had ever received a prescription of tamoxifen or raloxifene; this is fairly close to the PCP self-reported prescription rate at GHS. This reflects the poor adoption of breast cancer chemoprevention guidelines in primary care at GHS, which might be related to Geisinger's unique location, in rural Pennsylvania, as opposed to urban areas where other studies were performed. Given Pennsylvania's high incidence of breast cancer,[28] efforts to improve breast cancer prevention are needed.

We also analyzed the factors affecting PCPs breast cancer risk assessment and chemoprevention practices. Our findings suggested providers' experience of having diagnosed breast cancer in the past year was positively associated with performing risk assessment and prescribing chemoprevention agents. Similar findings were reported in a survey done in 2002, which showed higher annual numbers of breast cancer diagnoses promoted the prescription of both tamoxifen and raloxifene.[14] Having diagnosed breast cancer would help to improve providers' awareness of breast cancer, which may prompt PCPs to endorse chemoprevention; though this requires further study.

Notably, providers' personal experience with breast cancer in the family was not correlated with either breast cancer risk assessment or chemoprevention. This differs from findings from Armstrong et al and other studies, which showed physicians who had a family member with breast cancer were twice as likely to prescribe tamoxifen to high-risk patients.[14,15] Kaplan reported providers' sex or subspecialty could be a factor influencing provider's breast cancer risk reduction practices, with female gender and OB/Gyn specialty increasing the likelihood of prescribing raloxifene.[14] Our study did not replicate these findings, perhaps due to very few providers with chemoprevention experience in our sample.

In terms of the barriers to breast cancer risk reduction in primary care, our study revealed the top barriers were related to insufficient knowledge of breast cancer risk reduction. PCPs who were unaware of chemoprevention guidelines had higher odds (>3 times) for not using risk assessment tools in their clinical practices. Insufficient knowledge about breast cancer risk reduction is the most commonly cited barrier based on the limited evidence regarding physicians' attitudes towards their role in breast cancer risk reduction.[14] Studies focused on investigating PCPs' attitudes towards hereditary breast cancer and genetic testing showed similar finding,[29,30] indicating PCPs were also lacking expertise in genetic counseling of familial high-risk women. Our finding echoes findings from previous studies, which points out the importance of transmitting breast cancer chemoprevention knowledge from oncology society to primary care society.

Our study adds to the literature by investigating how to improve breast cancer chemoprevention practice from PCPs' perspective. Although about half of PCPs (48%) agreed they could provide breast cancer chemoprevention themselves if the electronic heath record systems could identify women at high risk of breast cancer, the majority of PCPs (85%) preferred to refer high-risk women to high-risk breast cancer clinics.

This study has several limitations. Although our response rate is consistent with other provider surveys, only about 40% of eligible providers participated.[13-15] Further, we only surveyed providers within the Geisinger Health System, a rural health care system, and our results may not be generalizable to physicians nationwide. Finally, we did not use clinical vignettes to assess PCPs' knowledge of breast risk assessment and risk reduction, nor did we conduct chart abstractions to validate providers' self-reports of risk assessment and reduction. Further research conducted in diverse health care systems and using data collection methods beyond self-report surveys will further add to the body of knowledge.

Our findings suggest that in rural areas of Pennsylvania, PCPs infrequently assess breast cancer risk and rarely prescribe chemoprevention drugs for risk reduction. Lack of knowledge in breast cancer risk assessment, chemoprevention drugs, and guidelines were the top three perceived barriers to adopting breast cancer chemoprevention in primary care. Most PCPs prefer referring patients to a high-risk breast clinic for breast cancer risk reduction. Our study suggests that PCP education on breast cancer prevention and establishing high-risk breast clinics may improve breast cancer chemoprevention uptake.

ETHICAL APPROVAL

ACKNOWLEDGEMENT

SOURCE OF FUNDING

CONFLICT OF INTEREST

Claire F Snyder, PhD; Consulting to Pfizer Oncology (June 2015), Honorarium from CaretMD (March 2016), Stock ownership of Immunomedics (current). The rest of authors report none.

REFERENCES

1. Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, et al. SEER Cancer Statistics Review, 1975–2009. National Cancer Institute, Bethesda, MD 2012.

2. Amir E, Goodwin PJ. Breast cancer chemoprevention gets personal. J Clin Oncol 2011; 29: 2296-2298.

3. Waters EA, McNeel TS, Stevens WM, Freedman AN. Use of tamoxifen and raloxifene for breast cancer chemoprevention in 2010. Breast Cancer Res Treat 2012; 134: 875-880.

4. Waters EA, Cronin KA, Graubard BI, Han PK, Freedman

AN. Prevalence of tamoxifen use for breast cancer chemoprevention among US women. Cancer Epidemiol Biomarkers Prev 2010; 19: 443-446.

5. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Nat Cancer Inst 1989; 81: 1879-1886.

6. Fisher B, Constantino JP, Wickerham DL, Redmond CK, Kavanah M, et al. Tamoxifen for prevention of breast cancer: Report of the National surgical adjuvant breast and bowel project P-1 study. J Natl Cancer Inst 1998; 90: 1371-1388.

7. Fisher B, Constantino JP, Wickerham DL, Cecchini RS, Cronin WM, et al. Tamoxifen for the prevention of breast cancer: Current status of the National surgical adjuvant breast and bowel project P-1 study. J Nat Cancer Inst 2005; 97: 1652-1662.

8. Barrett-Connor E, Mosca L, Collins P. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med 2006; 355: 125-137.

9. Rockwille. Breast cancer: Medications for risk reduction. US Preventive Service task force 2016.

10. Chlebowski RT, Col N, Winer EP, Collyar DE, Cummings SR, et al. American society of clinical oncology technology assessment of pharmacologic interventions for breast cancer risk reduction including tamoxifen, raloxifene, and aromatase inhibition. J Clin Oncol 2002; 20: 3328-3343.

11. Visvanathan K, Hurley P, Bantug E, Brown P, Col NF, et al. Use of pharmacologic interventions for breast cancer risk reduction: American society of clinical oncology clinical practice guideline. J Clin Oncol 2013; 31: 2942-2962.

12. Freedman AN, Graubard BI, Rao SR, McCaskill-Stevens W, Ballard-Barbash R, et al. Estimates of the number of U.S. women who could benefit from tamoxifen for breast cancer chemoprevention. J Natl Cancer Inst 2003; 95: 526-532.

13. Sabatino SA, McCarthy EP, Phillips RS, Burns RB. Breast cancer risk assessment and management in primary care: Provider attitudes, practices, and barriers. Cancer Detect Prev 2007; 31: 375-383.

14. Kaplan CP, Haas JS, Pérez-Stable EJ, Des Jarlais G, Gregorich SE. Factors affecting breast cancer risk reduction practices among California physicians. Prev Med 2005; 41: 7-15.

15. Armstrong K, Quistberg DA, Micco E, Domchek S, Guerra C. Prescription of tamoxifen for breast cancer prevention by primary care physicians. Arch Intern Med 2006; 166: 2260-2265.

16. Hoddinott SN, Bass MJ. The Dillman total design survey method: A sure-fire way to get high survey return rates. Can Fam Physician 1998; 32: 2366-2368.

17. Kenefick H, Lee J, Fleishman V. NEHI, Improving physician adherence to clinical practice guidelines 2008.

18. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999; 282: 1458-1465.

19. Neuhouser ML, Aragaki Ak, Prentice RL, Manson JE, Chlebowski R, et al. Overweight, obesity, and postmenopausal invasive breast cancer risk: A secondary analysis of the women's health initiative randomized clinical trials. JAMA Oncol 2015; 1: 611-621.

20. Friedenreich CM, Cust AE. Physical activity and breast cancer risk: Impact of timing, type and dose of activity and population subgroup effects. Br J Sport Med 2008; 42: 636-647.

21. Mackey S. Promoting lifestyle modification for cancer prevention. J Am Diet Assoc 2004; 104: 1568-1569.

22. Cuzick J, Forbes JF, Sestak I, Cawthorn S, Hamed H, et al. Long-term results of tamoxifen prophylaxis for breast cancer: 96 month follow-up of the randomized IBIS-I trial. J Natl Cancer Inst 2007; 99: 272-282.

23. Powles TJ, Ashley S, Tidy A, Smith IE, Dowsett M. Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. J Natl Cancer Inst 2007; 99: 283-290.

24. Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: Results from the MORE randomized trial. JAMA 1999; 281: 2189-2197.

25. Burke EE, Portschy PR, Tuttle TM. Prophylactic mastectomy: Who needs it, when and why. J Surg Oncol 2015; 111: 91-95.

26. Li X, You R, Wang X, Liu C, Xu Z, et al. Effectiveness of prophylactic surgeries in BRAC1 or BRCA2 mutation carriers: A meta-analysis and systemic review. Clinical Cancer Res 2016; 22: 3971-3981.

27. Advani P, Moreno-Aspitia A. Current strategies for the prevention of breast cancer. Breast cancer 2014; 6: 59-71.

28. American Cancer Society. Atlanta: Cancer facts and figures 2013.

29. Escher M, Sappino AP. Primary care physicians' knowledge and attitudes towards genetic testing for breast-ovarian cancer predisposition. Ann Oncol 2000; 11: 1131-1135.

30. Doksum T, Bernhardt BA, Holtzman NA. Does knowledge about the genetic of breast cancer differ between nongeneticist physicians who do or do not discuss or order BRCA testing? Genet Med 2003; 5: 99-105.

ADDRESS FOR CORRESPONDENCE:

Haiyun Wang, General Internal Medicine, MC 20-19, Geisinger Medical Center, 100 North Academy Avenue, Danville, PA, 17822, USA, Tel: (570) 214-9585; Fax: (570) 214-9519; E-mail: hwang1@geisinger.edu