Research Article

Cancer Prevention Research

Acceptability of Localized Cancer Risk Reduction Interventions Among Individuals at Average or High Risk for Cancer

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Abstract

Individuals at high risk for cancer, including those already diagnosed with premalignant lesions, can potentially benefit from chemopreventive interventions to reduce cancer risk. However, uptake and acceptability have been hindered due to the risk of systemic toxicity and other adverse effects. Locally delivered chemopreventive agents, where direct action on the primary organ may limit systemic toxicity, are emerging as an option for high-risk individuals. While a number of clinical trials support the development of chemopreventive agents, it is crucial to understand the factors and barriers that influence their acceptability and use. We conducted 36 focus groups with 198 individuals at average and high risk of breast/ovarian, gynecologic, and head/neck/oral and lung cancers to examine the perceptions and acceptability of chemopreventive agents. Participants' willingness to use chemopreventive agents was influenced by several factors, including perceived risk of cancer, skepticism around prevention, previous knowledge of chemopreventive agents, support from trusted sources of health information, participation in other cancer-related risk-reduction activities, previous experience with similar modalities, cost, regimen, side effects, and perceived effectiveness of the preventive intervention. Our findings indicate that individuals may be more receptive to locally delivered chemopreventive agents if they perceive themselves to be at high risk for cancer and are given the necessary information regarding regimen and side effects to make an informed decision. Clinical trials that collect additional patient-centered data including side effects and how these interventions fit into an individual's lifestyle are imperative to improve uptake of chemopreventive agents.

Introduction

Our ability to identify populations at higher risk of developing certain types of cancer has significantly improved over the past decade. For example, women with hereditary breast and ovarian cancer syndrome (HBOC) are at increased risk of developing breast, ovarian, and potentially other cancer types; individuals with Lynch syndrome are at increased risk of developing multiple cancer types including colorectal and endometrial cancers (1). In addition, our ability to detect cancer at earlier stages, including as precancerous lesions, has also significantly improved (2–4). These individuals at high risk for cancer or with early/precancerous lesions are excellent candidates to potentially benefit from prevention approaches.

A substantial number of studies have examined the use of chemopreventive agents, such as orally administered SERMs like tamoxifen and raloxifene, and aromatase inhibitors, in cancer risk reduction (5). Tamoxifen has been shown to reduce the overall incidence of invasive breast cancer among high-risk women by 43% in the Breast Cancer Prevention Trial (BCPT; ref. 6), 26% in the International Breast Cancer Intervention Study (IBIS-I; ref. 7), 16% in the Italian Randomized Tamoxifen Prevention Trial (8), and 22% in the Royal Marsden Study (9). In the Study of Tamoxifen and Raloxifene (STAR) where women were randomly assigned to receive either tamoxifen or raloxifene, there were an equal number of cases of invasive breast cancer, but the raloxifene group had a more favorable toxicity profile (10). For aromatase inhibitors in cancer prevention, the International Breast Cancer Intervention Study II (IBIS-II) investigated the efficacy and

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safety of anastrozole and found that invasive breast cancer was reduced by 53% (11), whereas the MAP.3 trial found that exemestane treatment reduced the incidence of invasive breast cancer by 65% (12). While these chemopreventive agents have shown great promise in reducing the risk of breast cancer, many studies have reported low acceptability, utilization, and adherence among individuals who would be good candidates for the risk-reducing medications (13–22).

Adverse effects associated with systemic exposure to chemopreventive agents continue to be of great concern, particularly as used in a relatively healthy population (23–26). As a result, recent research and clinical trials have focused on the development of chemopreventive agents and other risk-reducing interventions that are locally delivered to the primary organ of concern to reduce or possibly eliminate the systemic toxicities associated with oral administration. Examples include local transdermal therapy for the risk reduction of breast cancer, inhalation therapy for lung cancer, photodynamic light stimulation therapy for head and neck cancers, and a hormonal implant device for gynecologic cancers (27). While these local risk-reducing interventions hold promise for the effective prevention of certain cancers, it is essential that these efforts actually translate into increased acceptability among the general population, and in particular, those at high risk for specific cancers. Clinical trials of chemopreventive agents gather empirical data related to efficacy and toxicity; however, qualitative data is of critical importance to understanding the facilitators and barriers of acceptability of these interventions from a participant's perspective.

To better understand the factors that influence people's willingness to use chemopreventive agents, we examined the perceptions of locally delivered chemopreventive agents (e.g., topical application), systemically delivered chemopreventive agents (e.g., oral chemoprevention), and other preventive interventions (e.g., risk-reducing surgery) among individuals at average and high risk of three different groups of cancer: breast/ovarian cancers, gynecologic cancers, and head/neck/oral and lung cancers. We applied a qualitative study design to allow focus group participants to provide their perceptions and attitudes without *a priori* assumptions.

Materials and Methods

Design

We conducted a qualitative focus group study to explore the factors influencing the general acceptability and use of preventive interventions, including oral chemoprevention, locally delivered chemopreventive agents, and risk-reducing surgery, among individuals at both average and high risk of different types of cancer. Focus groups facilitate the synergy of group interaction resulting in the opportunity to generate large amounts of data from many participants at one time (28, 29). Furthermore, this method was chosen because it provides rich, contextual information and an in-depth perspective from participants that is not offered through other methods. The focus groups were conducted over the telephone. Telephone focus groups have been shown to enhance the sharing of sensitive information and group dynamics and interactions between participants are similar to those in face-to-face focus groups (30, 31). In addition, they allow for greater geographic diversity.

Recruitment

We used a purposive sampling strategy with the aim of recruiting individuals at both average and high risk for three groups of cancers: breast/ovarian, gynecologic, and head/neck/oral and lung cancers. The focus groups were stratified by cancer type, risk level (high, average), sex, and age, when applicable (see Table 1 for inclusion criteria). Participants were recruited through Focus Pointe Global

Table 1. Focus group inclusion criteria

Cancer type	Age	Sex	Average-risk group inclusion criteria	High-risk group inclusion criteria
Breast and ovarian cancers	30–45 45–60	F	Be a normal weight, without family history of cancer, and no abnormal screens	Have a *BRCA1/2* genetic mutation Have one or more of the following: first-degree relative(s) with breast or ovarian cancer; high breast density; ductal carcinoma *in situ* (DCIS); and/or *BRCA1/2* genetic mutation
Gynecologic cancers	30–39	F	Be a normal weight, without family history of cancer, and no abnormal screens	Have one of the following diagnoses: cervical intraepithelial neoplasia (CIN); high-risk human papillomavirus (HPV); endometrial intraepithelial neoplasia (EIN); complex atypical hyperplasia (CAH); polycystic ovary syndrome (PCOS); obesity; and/or Lynch syndrome
Lung/Head/Neck/Oral cancers	50–69	M F	Have had fewer than 100 cigarettes in their lifetime	Be a heavy smoker (30 pack-years)

Table 2. Focus group participant characteristics

	Breast/ovarian cancers ($n = 66$)		Gynecologic cancers ($n = 44$)		Lung/Head/Neck/Oral cancers ($n = 88$)		
Risk	**High**	**Average**	**High**	**Average**	**High**	**Average**	**Total**
# of Focus Groups	6	6	4	4	8	8	36
# of Participants	$n = 33\%$ (n)	$n = 33\%$ (n)	$n = 21\%$ (n)	$n = 23\%$ (n)	$n = 47\%$ (n)	$n = 41\%$ (n)	198% (n)
Sex							
Male	—	—	—	—	48.9% (23)	41.5% (17)	20.2% (40)
Female	100.0% (33)	100.0% (33)	100.0% (21)	100.0% (23)	51.1% (24)	58.5% (24)	79.8% (158)
Age							
Mean (range)	35.9 (30, 43) 51.1 (45, 58)	35.6 (30, 44) 51.4 (45, 60)	34.0 (30, 39)	34.3 (30, 39)	57.2 (50, 69)	55.3 (48, 68)	47.0 (30, 69)
Race/Ethnicity							
White	72.7% (24)	69.7% (23)	52.4% (11)	73.9% (17)	87.2% (41)	61.0% (25)	71.2% (141)
Black	21.2% (7)	15.2% (5)	23.8% (5)	8.7% (2)	8.5% (4)	22.0% (9)	16.2% (32)
Hispanic	3.0% (1)	6.1% (2)	14.3% (3)	8.7% (2)	4.3% (2)	4.9% (2)	6.1% (12)
Asian	3.0% (1)	3.0% (1)	—	8.7% (2)	—	7.3% (3)	3.0% (6)
Other/Mixed	—	6.1% (2)	9.5% (2)	—	—	4.9% (2)	3.0% (6)

recruitment firm, which sent an e-mail to their participant panel with a prescreening survey. Recruiters then followed up by phone with potential participants to confirm eligibility and availability for participation. Six participants were recruited for each focus group (see Table 2 for patient characteristics). E-mail and telephone reminders were sent the day before the focus group.

Data collection

Thirty-six focus groups were conducted with a total of 198 participants. The focus groups were conducted over two rounds to ensure data saturation, with 16 focus groups conducted in June 2017 ($n = 88$) and 20 focus groups conducted in February and March 2018 ($n = 110$). Focus groups consisted of 5–6 individuals per group and were facilitated by experienced moderators using a semistructured interview guide (Supplementary Data S1). The Moderator Guide consisted of open-ended questions with probes for deeper exploration of the following topics: cancer risk perception, knowledge of chemopreventive agents, acceptability of chemopreventive agents in general, and willingness to utilize locally delivered modalities. For each cancer type, participants were given specific descriptions of different chemopreventive agent modalities that were either currently available or under development (Table 3), and asked about factors that would influence their willingness to use the agent. The facilitator guide was updated between focus group rounds to include more detailed information about specific chemopreventive agent modalities under development.

Each focus group lasted approximately 60 minutes. All focus groups were audio-recorded, and an analyst took notes to capture information that could impact data interpretation and analysis. All participants received a gift card at the conclusion of the focus group. The research protocol was approved by ICF's institutional review board. Both written and verbal consent were obtained from participants prior to participation.

Data analysis

Focus group audio recordings were transcribed verbatim and analyzed using a thematic analysis approach including constant comparison, a standard qualitative analytic strategy used to identify similarities and differences across groups (28). The focus group, not individual participants, was the unit of analysis. The audio files from each focus group were transcribed verbatim and uploaded into the computer-assisted qualitative data management and analysis software program–NVivo 11. Multiple triangulation methods were used, including a triangulation of sources and analyst triangulation, to develop a comprehensive understanding of the participants' acceptability of chemopreventive agents. An initial taxonomy of concepts, or codes, was developed from the moderator's guide. A subset of transcripts was selected to validate the initial taxonomy, establish inter-rater reliability among analysts, and ensure consistent coding among three analysts (K.I. Coa, S.S. Kay, and J.L. Robinson for Round 1; S.S. Kay, J.L. Robinson, and B. Tennant for Round 2). The remaining transcripts were analyzed using line-by-line coding, and the analysts routinely met to discuss any discrepancies and refine the taxonomy to address any gaps. The finalized taxonomy/codebook is presented as Supplementary Data S2. Once coding was complete, the data were explored to identify the similarities and differences within and across groups, as well as to understand the relationships between the various codes.

Results

Participants

The majority of participants were women (79.8%), which is reflective of two of the cancer groups being specific to the female anatomy (Table 2). Most participants were White (71.2%), although some groups were more diverse than others (range 52.4%–87.2%). Black participants were the second most represented (16.2%), followed by Hispanic participants (6.1%). The average age of participants

Table 3. Interview guide modality descriptions

Cancer type	Modality	Focus group round 1 description	Focus group round 2 description
Breast and ovarian cancers	Pill	A pill taken daily for 5 years (Tamoxifen). Possible side effects: hot flashes, blood clots, cataracts, and elevated risk of uterine cancer.	No changes
	Topical agent	A cream or gel to be applied to one's breasts. Possible side effects: irritated skin or rash.	Similar to hand sanitizer or clear glue. Possible side effects: hand sanitizer–sensitivity to sunlight and irritated skin (burning/itching) or rash for 5–10 minutes after application; clear glue–rash for 7 days after initially starting application.
	Surgical options	Discussed as an alternative to chemopreventive agents.	No changes
Gynecologic cancers	Hormonal implant or ring	Similar to a hormonal implant, like Mirena, or ring, like NuvaRing. Possible side effects: headache, acne, breast tenderness, changes in your period, changes in your mood, weight gain, ovarian cysts, and/or cramping.	No changes
	Topical agent	A cream or gel to be applied to one's cervix. Possible side effects: irritation or rash.	No changes
	Surgical options	Discussed as an alternative to chemopreventive agents.	No changes
Lung/Head/Neck/Oral cancers	Aerosolized drug	Similar to an inhaler or nebulizer. Possible side effects: coughing.	A small device (similar to an asthma inhaler) that is 6 inches in height and weighs under 8 ounces.
	Light stimulation therapy	A handheld device that emits light to a targeted area of one's body. Possible side effects: sensitivity to light, burns, swelling, pain, scarring, coughing, trouble swallowing, stomach pain, and shortness of breath.	Going to a clinic for one light-therapy session, with the possibility of needing a second treatment several months later.
	Topical agent	A mouthwash that can be swished around in one's mouth and/or swallowed. Possible side effects: irritated skin or rash in mouth.	No changes

was 47 years. All participants resided in the United States with close to a third of participants coming from the Northeast (29.1%), followed by the South (25.5%), Midwest (23.6%), and West (21.8%).

Key findings

Factors that influenced participants' willingness to use preventive interventions fell into two categories: general factors and modality-related factors. The general factors influencing participants' overall willingness to use preventive interventions included: perceived risk of cancer (those with increased risk of cancer were more open to preventive options), evidence supporting effectiveness, skepticism around prevention, familiarity with cancer treatment, previous knowledge of chemopreventive agents, support from a trusted source of health information, participation in other cancer risk-reduction activities, previous experience with similar modalities, and cost. The modality-related factors included concerns around the modality's regimen, side effects, and perceived effectiveness.

General factors

Risk of cancer. Participants, particularly those at average risk for cancer, cited that knowing or perceiving themselves to be at risk for a particular type of cancer would increase their willingness to use chemopreventive agents.

"If it was something in the family, then I would say OK. But if that wasn't the case, I don't believe in meddling with something that's not broke. Don't fix it. Don't go around meddling and trying to do something that doesn't need to be reduced, if you are not predisposed to it." – Average-Risk Breast/Ovarian Cancers (Age 30–45) Focus Group (FG) Participant.

Participants in the breast/ovarian and gynecologic focus groups reported that they would need to be at high risk of cancer (e.g., a "definite" possibility or if they received a "prediagnosis") to consider prophylactic surgery, such as mastectomy or hysterectomy.

Evidence supporting effectiveness. Most participants reported that seeing evidence of effectiveness would influence their willingness to use a chemopreventive agent. More specifically, they wanted broad acceptance of the chemopreventive agent by the medical community and a means to monitor its effectiveness. Participants defined effectiveness in various ways, including seeing indicators of the medicine's effectiveness in their health and well-being and the medicine being well beyond the experimental, or "guinea pig," stage with a large amount of research and/or evidence of success.

"If we're talking about a medication that is preventative, how do you monitor that? I'm not somebody who has ever taken any kind of a test. I know that there are DNA-like tests to see what your risk factor is. But if I haven't already been diagnosed with cancer and I'm just taking a preventative medication, how do I know that the inhaler is working to prevent me from getting lung cancer? What are the indicators that the medication is working? I'm assuming that they would monitor me for side effects, but I don't understand what the indicators would be to say, oh, this medication is working." – Average-Risk Head/Neck/Oral and Lung Cancers Female FG Participant.

In general, high-risk participants were willing to accept a lower threshold of effectiveness compared with average-risk participants (40%–60% vs. ≥70%–90%), with high-

risk participants stating that they would consider the side effects and cost before the degree of efficacy when considering their willingness to use a chemopreventive agent. For those individuals who would consider prophylactic surgery, most expected their risk to be eliminated, or a high degree of effectiveness compared with the other preventive interventions.

Skepticism around cancer prevention. Many participants, particularly those at average risk, questioned the very idea that medicine can reduce one's risk of cancer, which inevitably impacted their willingness to use a chemopreventive agent.

"The claim of cancer preventing or cancer curing drugs have long been in the realm of the National Enquirer. . .I just haven't seen anything, and I'm 63, in my life that will prevent or cure cancer. Now, I'm not saying that there isn't, but I mean it's not, it's not a matter of public knowledge, and I think I'm pretty well informed, and I haven't seen it. I think as smokers, it's natural that we hold out the possibility that there will be a drug that comes by and saves us, like the white knight, but I just don't think that's in the cards." – High-Risk Head/Neck/Oral and Lung Cancers Male FG Participant.

Familiarity with cancer treatment. Participants reported that their familiarity and/or experience with cancer, such as seeing a friend or family member go through a cancer scare, cancer treatment, and/or dying from cancer, would influence their willingness to use a chemopreventive agent.

Regardless of their familiarity with cancer (or lack thereof), many participants perceived the side effects from chemopreventive agents to be miniscule in comparison with having cancer. However, a few participants discussed a hypothetical threshold for side effects, and being less willing to use a chemopreventive agent if the side effects mirrored the side effects of cancer treatment too closely.

"I watched my father go through some extreme burning with some of the radiation therapy that he was receiving for his melanoma. . .he had extreme difficulty swallowing. The only thing he could eat for a while was yogurt, and even that, he had to force down. . .I would be willing to go through some of it, to tolerate some of it, but not to the point where it completely altered my lifestyle and eating habits. That type of thing I would reserve if I was actually being treated for cancer, and not as preventative." – Average-Risk Head/Neck/Oral and Lung Cancers Male FG Participant.

Previous knowledge of chemopreventive agents. The majority of participants reported little to no prior knowledge of chemopreventive agents. High-risk participants in the breast/ovarian and gynecologic cancers focus groups who were at increased risk for cancer due to medical factors (e.g., *BRCA1/2* carrier) were more likely to report knowledge of chemopreventive agents, as well as surgical options. Chemopreventive agents and/or preventive interventions mentioned include the human papillomavirus vaccination (Gardasil), tamoxifen, and prophylactic surgery (e.g., mastectomy). More specifically, most high-risk participants in the breast/ovarian and gynecologic cancers focus groups cited their awareness or knowledge of chemopreventive agents and/or preventive interventions came through conversations with a healthcare professional about the different options available for reducing their risk. In addition, some women reported hearing about prophylactic surgery through the media, and a few participants had already undergone prophylactic surgery.

Support from trusted sources of health information. Participants most often reported that they would consult their healthcare provider for more information or help in making a decision about whether or not to take a chemopreventive agent. Participants cited that receiving a recommendation and/or support from their doctor would influence their willingness to use a chemopreventive agent.

"I think a lot of my own personal decision-making process is based on a conversation I would have with a doctor that I trust, and if he thinks it's a good idea, I would just do it. Even if it was a smaller percentage of improvement, or likely improvement of my health, I'd give it a shot." – Average-Risk Head/Neck/Oral and Lung Cancers Male FG Participant.

Other sources of information included the internet and media (e.g., cancer-specific organizations, medical authorities, regulatory agencies), as well as family and friends.

Participation in other cancer risk-reduction activities. Most participants reported engaging in a number of cancer risk-reduction activities, such as healthy lifestyle habits (e.g., diet and exercise), limiting alcohol and tobacco use, outdoor skin care (sunburn prevention through sunscreen use, limiting time in/staying out of the sun, wearing protective clothing, and not using tanning beds), routine medical appointments, alternative methods (e.g., colon cleanse), and knowing family history and one's body (when something does not feel right). In general, average-risk participants reported more engagement in risk-reduction activities compared with high-risk participants and believed their participation lowered their risk of cancer. While some high-risk participants cited more well-known medical and lifestyle factors that put them at high risk for cancer (e.g., smoking, family history), many did not discuss risk factors beyond being a BRCA *1/2* carrier and HPV. In addition, a number of participants, more frequently those at high risk for cancer, cited feelings of helplessness in their ability to prevent cancer.

"I'm a little bit biased because I've seen people who have been healthy, ate good, and still got cancer. So I feel like it's really nothing that you can really do. I just think it's one of those things

that unfortunately happens. . .I had a friend who had lung cancer. Never smoked a day in her life, and it's severe. I think that all those things are wonderful things, but I just don't think there's much you can do." – High-Risk Gynecologic Cancers FG Participant.

Previous experience with similar modalities. Many participants described prior experience and familiarity with medicines and/or common modalities similar to chemopreventive agents (e.g., pills, inhalers, mouthwash, lotions). As a result, participants felt comfortable in their ability to fit these types of intervention regimens into their daily routine. However, if participants had negative experiences with similar medicines or modalities, they were less willing to use a chemopreventive agent.

Cost. Many participants described cost as a constraining factor, but most could not accurately pinpoint an amount they would be willing to pay for a chemopreventive agent. Participants felt that their decision depended on the cost in the context of other factors, such as regimen, effectiveness, and one's risk of cancer. Most participants wanted more information about insurance coverage and possible out-of-pocket expenses.

Modality-specific factors

Participants shared perceptions about the modalities' regimens, possible side effects, and effectiveness (see Table 4 for detailed feedback by modality). Generally, participants preferred regimens perceived to be familiar or convenient, side effects that were minor and did not simulate having cancer or undergoing cancer treatment, and modalities that logically "seemed" to be effective (e.g., participants perceived the inhaler to be effective because it delivered medicine directly to the lungs). More specifically, the participants expressed concern for how locally delivered chemopreventive agents might impact their daily lives. For example, they discussed apprehension regarding severity and duration of local responses (e.g., skin rashes or coughing) and how these might impact their daily routines.

Modality comparison and preference. When participants were asked to choose their preferred modality, participants often weighed side effects against perceived efficacy and convenience of regimen when making their decision. The breast/ovarian cancer focus groups' preference varied, citing the ease and convenience of "popping a pill," but noting that the topical agent seemed "less risky" with fewer possible side effects. Many participants, especially average-risk participants, felt more comfortable with other risk-reduction activities, such as maintaining a healthy diet and exercise regimen, in comparison with the other preventive inventions.

"You know for me, it's the idea of health in a pill. You just have to pop a pill, and everything will be fine. You know? To me, that is such a lie that has been told to people by the pharmaceutical industry. . .Health isn't about taking pills to make yourself feel better. . .I get that there are instances, like we've been talking about people that have a real genetic risk. And I think in those places, pills are important. But for the majority of people, I think it's a trap to think I can just take this pill and do whatever I want, and be healthy." – Average-Risk Breast/Ovarian Cancers (Age 30–45) FG Participant.

Within the gynecologic cancer focus groups, participants overwhelmingly preferred the topical agent (gel/cream) citing that it was not as invasive and left them feeling in control.

"I think that if I did the cream and I started to notice that I was having effects, it's easier for me to just stop the cream versus having to go to the doctor if I feel like I'm having effects from the insert to have to go to the doctor to have the insert removed. I just think it gives me more control." – High-Risk Gynecologic Cancers FG Participant.

The head/neck/oral and lung cancer focus groups preferred the topical agent (mouthwash) over light therapy stimulation during the first round of focus groups due to its perceived simplicity and ease in being able to fit it into their existing daily routines, such as brushing their teeth. However, when the light stimulation therapy modality was presented as a one-time event, participants' preference shifted to this modality due to its perceived convenience (achieving risk reduction through a one-time event, *versus* a series of events).

Although many participants expressed a preference for one modality over another, they emphasized that the actual modality did not influence their willingness as much as other factors, such as risk of cancer, effectiveness, and possible side effects.

"Whether it's a pill, or an inhaler, or mouthwash, or whatever, it wouldn't matter. What is my risk, am I high risk? And the side effects for it. I think that's the main thing I would watch out for and be concerned about." – Average-Risk Female Head/Neck/Oral and Lung FG Participant.

Discussion

These focus groups revealed that perceived risk of cancer, skepticism around prevention, familiarity with cancer treatment, previous knowledge of chemopreventive agents, support from trusted sources of health information, participation in other cancer risk-reduction activities, and cost, as well as the regimen, side effects, and perceived effectiveness of the preventive interventions, are factors that influence average and high risk participants' willingness to use chemopreventive agents. Generally, participants perceived most chemopreventive agents (pills,

Table 4. Perceptions of modality-specific regimen, possible side effects, and effectiveness

Modality-specific factors of willingness to use chemopreventive agents			
Modality	**Perceptions of regimen**	**Perceptions of side effects**	**Perceptions of effectiveness**
Pill (for breast/ovarian cancers)	- Noted ease and convenience of being able to fit into and/or combine with existing daily routines (e.g., brushing teeth, taking birth control pill) - Expressed uncertainty in their ability to carry out a daily pill regimen for 5 years - Concerned about impact of missing a dose	- Expressed most concern for increased risk of uterine cancer and blood clots – perceived as too serious for preventive purposes	- Considered pills not as effective as modalities that delivered medicine directly to the organ(s) of concern - Perceived risk-reduction activities, such as diet and exercise, to be more effective
Topical agent – gel/cream (for all cancers)	- Perceived as easy and convenient - Expressed confidence in being able to fit it into their existing daily routines (e.g., beauty/skin care regimen) indefinitely - Preferred regimen that did not require application outside the home - Wanted to know more about the application process, such as whether they could take a shower after applying or if reapplication would be necessary after exercise or sweating	- Concerned about the severity and duration of the irritated skin and rash - Worried about an unpleasant application process or impact on their skin (e.g., messy application process, leaves a sticky residue, dries out their skin, skin smells during/after application, stains clothing) - Noted that sensitivity to light was not a problem as long as they could still enjoy activities outside - Concerned for others that may come in contact with topical agent (e.g., intimate encounters with partner, child sleeping on their chest)	- Skeptical of how a gel/cream could be effective at preventing cancer without serious side effects, such as interfering with hormones
Topical agent – mouthwash (for head/neck/oral cancers)	- Perceived as simple and convenient - Cited ease in being able to fit into and/or combine with existing daily routines (e.g., brushing teeth) - Expressed confidence in being able to adhere to regimen indefinitely - Felt that swishing and/or rinsing was less invasive than swallowing	- Worried about how the rash would impact their ability to breathe, communicate, and eat - Apprehensive about taste (e.g., leaves a bad taste in mouth, gag reflex effect) - Concerned about the severity and duration of the irritated skin or rash, and if it would have a "domino effect" leading to sores or blisters, and possibly infections	- Skeptical of how a mouthwash could be effective at preventing cancer
Hormonal implant or ring (for gynecologic cancers)	- Unwillingness stemmed from negative experiences with birth control (e.g., intrauterine device, vaginal ring) - Concerned about invasive nature of the modality, citing their fear of having a foreign object inside their body - Expressed comfort in having a doctor involved to properly insert the device - Apprehensive about taking the power and/or control out of their hands	- Concerned about increasing side effects already experienced through menstruation, birth control, or other gynecologic conditions (e.g., PCOS) - Disliked the possibility of weight gain - Alarmed about the possibility of ovarian cysts and hormones' impact on fertility, pregnancy, and breastfeeding	- Considered more effective because a healthcare provider inserts the device
Aerosolized drug (for lung cancer)	- Felt comfortable using due to prior experience and/or familiarity with an inhaler (e.g., asthma, allergies) - Noted the convenience factor of being able to carry it with you - Hesitant (more so average-risk participants) to carry small aerosolized drug device - Preferred frequency of use varied greatly - High-risk participants expressed willingness to increase frequency of use for a shorter duration of time (e.g., daily use for 30 days) or indefinite use	- Perceived to have fewer side effects (compared to a pill) - Concerned about severity and duration of cough (e.g., impact on sleeping, interference at work) - Some high-risk participants familiar with coughing due to smoking and COPD were worried about increased coughing - Other participants were unconcerned and considered it mild in the context of cancer	- Considered more effective due to local delivery and minimal impact on other organ systems
Light stimulation therapy (for head/neck/oral cancers)	- Liked the convenience of a one-time treatment - Concerned about accessibility to a clinic - Expressed comfort in knowing a healthcare provider would be involved - Unconcerned about need to take a pill along with the light therapy - Wanted to know more about the regimen (e.g., length of session) and type of light being used	- Concerned about "long laundry list" of possible side effects - Alarmed about possible burning and/or scarring (especially to their face) - Frightened by shortness of breath and trouble swallowing - Some interpreted side effects to be specific to their eyes (e.g., burning, irritation, itching) and worried about eyesight - Worried about light sensitivity impacting their ability to be outdoors - Found side effects to be similar to cancer treatment	- Wanted to see tangible evidence of effectiveness

(Continued on the following page)

Table 4. Perceptions of modality-specific regimen, possible side effects, and effectiveness (Cont'd)

Modality-specific factors of willingness to use chemopreventive agents			
Modality	**Perceptions of regimen**	**Perceptions of side effects**	**Perceptions of effectiveness**
Prophylactic surgery	- Viewed as a "last resort" - Needed to be at high risk in order to consider	- Concerned about surgical complications and recovery time - Expressed hesitation (especially 30–45 year olds) due to desire to have children and breastfeed - Worried about impact on hormones and sexual pleasure - Noted emotional impact of a mastectomy, but found benefit in being able to consider reconstructive surgery	- Expected significant reduction and/or elimination of cancer

Abbreviations: COPD, chronic obstructive pulmonary disease; PCOS, polycystic ovary syndrome.

topical agent, aerosolized agent, and light therapy) as convenient and familiar, while hormonal implants and prophylactic surgery were perceived as invasive.

Of note, participants questioned how efficacy could be measured in the prevention space, and whether biomarkers existed to indicate that a chemopreventive agent was working. There are a number of biomarkers that may serve as endpoints for evaluating chemopreventive efficacy (32). In some cases, the presence of preinvasive lesions that predispose women to their associated malignancy, such as ductal carcinoma *in situ* (DCIS) in breast cancer or endometrial intraepithelial neoplasia (EIN) in endometrial cancer, can be utilized both as a measurement of risk as well as a potential endpoint of preventive efficacy. Cancer-associated biomarkers such as Ki-67 tissue expression, circulating markers such as estrogen or progesterone, and gene expression profiling may also be useful as indicators of efficacy since these factors are commonly deregulated during progression. However, progression of preneoplastic lesions and expression of cancer-associated biomarkers vary greatly between cases, and access to tissue for accurate measurement is challenging, limiting the use of these endpoints for determining prevention efficacy (32). Moreover, clinical biomarker validation requires large-scale clinical trials with definitive cancer endpoints. Therefore, there remains a great need to develop validated biomarkers of response to preventive interventions that reflect clinical benefit, mirroring the model of measuring/controlling blood pressure to reduce risk of cardiovascular disease (33–35).

Participants' perceptions of local delivery efficacy varied; they believed that an agent delivered directly to the organ of concern would be more effective than a systemic intervention but were skeptical of how topical agents in particular could result in risk reduction. In fact, using topical agents in breast disease has been shown to deliver high concentrations in the breast with longer retention, decrease proliferation to the same degree as oral delivery, with low systemic exposure (36). There are currently 12 agents approved by the FDA for cancer risk reduction, although uptake of these agents is still not optimal (27). Pharmacologic studies of these agents suggest that small, lipophilic molecules with good dermal permeation are excellent candidates for topical application in cancer prevention (27, 36). Moreover, direct application of active metabolites of preventive or therapeutic agents, bypassing metabolism and toxicity, has shown promising results. This improved understanding of the pharmacologic characteristics of an effective agent could lead to an expansion of options for local delivery of additional chemopreventive agents.

An important finding from our focus groups was the skepticism associated with cancer prevention. Some participants likened the concept to tabloid fodder. This is particularly striking in an age where "magic/silver bullets" and promises of cures are evident in all aspects of media. And while numerous studies have demonstrated an increase and lasting awareness of risk and options for risk reduction since 2013, in part attributable to the "Angelina Jolie Effect" (37–41), many of the participants expressed skepticism regarding prevention in general and considered surgery as a "last resort" when considering preventive interventions. Moreover, many participants, particularly those at average risk, expressed unrealistic expectations of acceptable risk reduction with suggested rates (e.g., 70%–90%) that far exceeded more widely used preventive agents [e.g., statins, which reduce low-density lipoprotein levels by 30%–63% (42), or aspirin, which reduces the risk for nonfatal myocardial infarction by 22% (43)]. Scientific data indicates that >50% of cancers are preventable mainly through lifestyle interventions (e.g. smoking or diet), but also through medical interventions (e.g., vaccinations, surgery; ref. 44). Furthermore, studies have demonstrated that risk awareness in an important factor in influencing attitudes and behaviors related to cancer interventions (45). The results of our study suggest that average and even high-risk individuals are not adequately informed of risk assessment tools or evidence supporting cancer prevention. To determine where the breakdown of communication stems from, future studies should evaluate physician perceptions and behaviors regarding risk assessment and cancer prevention.

Our findings that most of the average-risk participants had minimal knowledge or awareness of chemopreventive agents and that many participants reported that they would rely on the recommendation of their healthcare provider support numerous studies that demonstrated that physician recommendation is a major factor associated

with decision making regarding risk reduction and chemoprevention (26, 46). A meta-analysis published in 2016 aimed to determine the psychological, clinical and demographic factors associated with use of breast cancer preventive agents demonstrated that uptake was low across 26 different studies [16.3% (95% CI 13.6–19.0), range 0–54.9%], with physician recommendation associated with higher uptake (46). These findings indicate that physicians serve as a significant point of entry for conversations about chemopreventive options. However, while many physicians have reported using risk assessment models, only a minority have reported prescribing chemopreventive agents (9%–31%; refs. 47–50). The most commonly reported barriers include lack of knowledge of chemopreventive agents and effects and uncertainty of health risk assessment. While a larger survey across clinical disciplines could better elucidate the usage patterns, perceptions, and barriers in the chemoprevention space, these findings demonstrate that patient and physician education regarding the regimens, risks, and benefits of chemopreventive agents is vital to improving acceptability.

This study was designed as a semistructured qualitative study to identify issues that high- and regular-risk individuals consider when making decisions regarding prevention interventions, while allowing for spontaneous or unprompted responses and discussion. The results are then systemically analyzed, which provides the opportunity to discover issues or topics organically, rather than influencing the responses. The advantages of qualitative focus group studies include: ability for depth and detailed data; data collection can be redirected or guided by researchers in real time (e.g., a question can be clarified if a participant does not understand, or an answer can be broadened); research findings are typically easy to understand and digest for a wide range of audiences; focus group studies allow for "group think" where participants can build off of one another's responses.

While a major limitation of these types of qualitative studies is the inability to undertake quantitative or statistical analyses of the results, these studies have the benefit of revealing patient perceptions that may not have been considered *a priori*. These newly discovered perceptions/ideas can then be explored in quantitative, hypothesis-driven future studies. Other potential limitations of focus group studies are that responses may be affected by group dynamics (e.g., with more outspoken members of the group steering the conversation) or misinformation (e.g., different perceptions of risk, efficacy, or severity of side effects); bias of the moderator; and responses might not be representative as they reflect volunteers who were willing to participate in focus groups.

We sought to overcome these potential limitations by having content experts help design the Moderator's Guide while the moderators themselves were not content experts. Trained moderators facilitated each focus group. Moderators were experienced in managing group dynamics and engaging all participants in the discussion. The semistructured moderator's guide was designed to guide the discussion and conclude in a timely manner, while also allowing space for the moderator to follow-up and/or ask additional questions when necessary.

The race distribution of our study population reflects the U.S. population. However, because the majority of our participants were white (71.2%), some perspectives relevant to non-White populations may have been missed. These interviews were conducted over the phone to allow for more flexibility, anonymity, and to reach a greater range of participants from across the country; but it also meant that the moderator could not ensure that participants had their entire focus on the conversation. It also influenced the group dynamic since participants were not physically present, could not see others' body language or facial expressions, or may have been hesitant to speak up since there were multiple people on the phone. Also, the moderators were limited in describing the options for the risk-reducing medications to verbal descriptions and could not use any visual aids to present the information or physical examples.

Our findings suggest that participants desire detailed and nuanced information when making a decision about whether they would use a particular chemopreventive agent (Table 4). These details should also include updated evidence of risk assessment measurements as well as efficacy of cancer prevention interventions currently utilized in the clinic. Furthermore, participants' perceptions and preferences varied greatly, suggesting that individuals weigh costs and benefits differently and a "one size fits all" approach will not work. Therefore, it is imperative that clinical trials are designed to better capture the regimen specifics (e.g., convenience, flexibility, invasiveness, familiarity, sensory factors) and side effects (e.g., risks, adverse events, other patient-reported outcomes) to provide the medical community, especially first-line providers, the nuanced information their patients want to know when considering chemopreventive agents.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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