Review

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Breast Cancer Prevention: Current Approaches and Future Directions

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ABSTRACT

The topic of breast cancer prevention is very broad. All aspects of the topic, therefore, cannot be adequately covered in a single review. The objective of this review is to discuss strategies in current use to prevent breast cancer, as well as potential approaches that could be used in the future. This review does not discuss early detection strategies for breast cancer, including breast cancer screening. The breast is the most common site among women worldwide of noncutaneous cancer. Many clinical and genetic factors have been found to increase a woman's risk of developing the disease. Current strategies to decrease a woman's risk of developing breast cancer include primary prevention, such as avoiding tobacco, exogenous hormone use and excess exposure to ionizing radiation, maintaining a normal weight, exercise, breastfeeding, eating a healthy diet and minimizing alcohol intake. Chemoprevention medications are available for those at high risk, though they are underutilized in eligible women. Mastectomy and/or bilateral oophorectomy are reasonable strategies for women who have deleterious mutations in genes that dramatically increase the risk of developing cancer in either breast. There are a variety of strategies in development for the prevention of breast cancer. Personalized approaches to prevent breast cancer that are being developed focus on advances in precision medicine, knowledge of the immune system and the tumor microenvironment and their role in cancer development. Advances in our understanding of how breast cancer develops are allowing investigators to specifically target populations who are most likely to benefit. Additionally, prevention clinical trials are starting to evaluate multi-agent cancer prevention approaches, with the hope of improved efficacy over single agents. Finally, there is a push to increase the use of chemopreventive agents with proven efficacy, such as tamoxifen and raloxifene, in the prevention of breast cancer.

Keywords: Breast cancer, biomarkers, carbohydrates, proteins, DNA, RNA

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Introduction

While breast cancer death rates increased by 0.4% per year in the United States (U.S.) between 1975 and 1989, between 1989 and 2015 they decreased by 39%, averting 322,600 deaths (1). There has not been a similar decrease in breast cancer incidence. The incidence of breast cancer is increasing in the developing world due to increased life expectancy, increased urbanization and the adoption of western lifestyles (2). There is an emerging epidemic of obesity related cancers, including breast cancer, in many parts of the developed and developing world. The incidence of obesity related cancers (other than those of the colon and rectum) increased in the U.S. by 7 percent between 2005 and 2014, while the rates of non-obesity related cancers declined during that time (3). About 631,000 people in the U.S. were diagnosed with a cancer associated with overweight and obesity in 2014 (3).

The prevention of breast cancer depends on targeting factors that increase risk. Many, but not all of these risk factors can be modified. Those that can be modified include diet; exercise; avoidance of certain things such as tobacco, exogenous female hormones, ionizing radiation, and alcohol in excess; pregnancy and nursing. An important question when discussing breast cancer prevention is which individuals to target. In general, greater focus has been placed on strategies to decrease risk among those at the greatest risk of developing breast cancer. For high risk women, two chemoprevention medications have been approved by the U.S. Food and Drug Administration (FDA), and a third recommended by some governing bodies for use. Surgery has also been recommended for certain subsets of women who are genetically at increased breast cancer risk.

Risk factors are inherited, histopathologic or environmental, each of which is important. Strategies to decrease environmental risks generally focus on directly addressing the environmental factor, whereas genetic and histopathologic risks, which cannot so easily be altered directly, are addressed indirectly, such as through altering known drivers to breast cancer, such as estrogen and its receptor through chemoprevention, or by surgical extirpation of the organ(s) at risk. Mammographic breast density (MBD) also influences breast cancer risk. MBD is appears to be influenced by genetics (4), age and body mass index (5).

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There are a variety of risk assessment tools available, some of which require information on breast cancer (*BRCA*) gene mutation status, and others which do not but rather focus on clinical and histopathologic factors which influence risk (6). The Gail breast cancer risk assessment tool (BCRAT) is the tool most commonly used in the U.S. to estimate a woman's risk of developing breast cancer. This tool was used to determine eligibility in two large U.S. breast cancer prevention trials (the first evaluating tamoxifen, the second tamoxifen vs. raloxifene) (7). It incorporates a variety of clinical and histopathologic factors. Two European breast cancer prevention trials (the first evaluating tamoxifen, the second anastrozole) used the Tyrer-Cuzick risk assessment tool, which incorporates genetic and clinical breast cancer risk factors (7).

Scientists have identified some of the genetic mutations which drive the development of breast cancer, but we know relatively little of genetic alterations which work together, or in concert with environmental alterations, to promote breast cancer development. Some of the proven or potential driver genetic alterations, including *BRCA 1* and *2, TP53, PTEN, STK11, CDH1, PALB2, CHECK2, ATM, NBN,* and *NF1* (8), are included in commercially available risk assessment panels. Genetic counseling can be provided to discuss detection of one or more alterations in a driver mutation, as well as the implications of an identified deleterious mutation and a patient's options.

Male breast cancer (MBC) accounts for fewer than 1% of all cancers in men and is less than 1% as common as female breast cancer (9). Due to the relative rarity of MBC, far less is known about what causes the disease, and chemoprevention studies have generally excluded men from enrollment. Nonetheless, limited studies have provided evidence for the causes of MBC. A report which pooled data from 11 case-control and 10 cohort studies, including 2,405 men with and 52,013 men without breast cancer, demonstrated that risk factors for MBC include obesity (odds ratio-OR=1.3), diabetes (OR=1.19), Klinefelter syndrome (OR=24.7), and gynecomastia (OR=9.78) (10). Many of these factors lead to elevated levels of circulating estrogen. Family history is also an important risk factor for MBC. Deleterious mutations in *BRCA1* and *2* are known to significantly increase the risk of MBC. Lifetime risk of developing MBC is 1–5 % for *BRCA1* and 5–10 % for *BRCA2* mutation carriers, compared with a risk of 0.1% in the general male population (9).

Currently Accepted Targets for Breast Cancer Prevention

1. Primary prevention

A. Dietary modification

Obesity is a common cause of many cancers, including those of the breast, endometrium, ovary, prostate, liver, gallbladder, kidney and colon (11). How specific foods influence breast cancer risk, independent of weight gain or loss, is less certain (12). Obesity is associated with a higher risk of premenopausal estrogen receptor negative breast cancer and triple negative breast cancer (TNBC), with two meta-analyses of women with TNBC demonstrating an 80% and 43% higher risk of developing TNBC, respectively, in obese than in non-obese premenopausal women (13). Between 2011-2014 over one third (36.5%) of U.S. adults were reported to be obese (BMI≥30) (14), with rates higher among women than men. The prevalence of obesity was lowest among Asian (11.7%) and highest among black (48.1%) adults (14). The prevalence of obesity among children aged 2-10 years was 17% (14). The prevalence of obesity continues to increase among adults (from 30.5% in 1999 to 37.7% in 2014), though youth obesity may be leveling off (14).

Many U.S. adults who are not obese are overweight (BMI 25-29.9). Estimates in 2015 suggested that 40% of men (36.3 million) and 29.7% of women (almost 28.9 million) were overweight. Combined with the percent of obese individuals, in 2015 more than two thirds of U.S. adults were overweight or obese (15). These trends are also seen in other parts of the world, and worldwide obesity has nearly tripled since 1975 (11). In 2016, the World Health Organization reported that 1.9 billion adults and 381 million children aged 2-19 years were overweight or obese (11).

B. Exercise

Exercise appears to be safe for most breast cancer patients, and improves their physiological and psychological well-being (16). Assessment of the benefits of exercise in the prevention of breast cancer are often confounded by the effects of concomitant weight loss or gain. A meta-analysis of prospective studies which evaluated the association between physical activity and breast cancer risk involving 63,786 individuals demonstrated a 12% reduction in risk among those who were physically active vs. those who were not (17). Stronger associations with physical activity and breast cancer risk were found for subjects with a BMI <25 (hazard ratio: HR=0.72), premenopausal women (HR=0.77), and estrogen and progesterone receptor-negative breast cancer (HR=0.80).

C. Tobacco and alcohol

Tobacco use is a leading cause of cancer incidence and death from cancer (18). Tobacco use causes cancer of the lung, larynx, mouth, esophagus, throat, bladder, kidney, liver, stomach, pancreas, colon and rectum, and cervix, as well as acute myeloid leukemia. Studies evaluating a possible association of tobacco use with breast cancer have demonstrated mixed results. This may be due to the confounding of alcohol use. Most reports indicate that alcohol use increases breast cancer risk (19). A longitudinal study was conducted by the American Cancer Society involving over 70,000 women with a median follow-up of 13.8 years in which concomitant alcohol use was considered. The analysis demonstrated that breast cancer incidence was 24% higher among smokers than non-smokers and 13% higher in former smokers than non-smokers (20), with a stronger association between smoking and breast cancer risk among women who started smoking before the birth of their first child. The positive association between smoking and breast cancer risk was seen in current or former alcohol drinkers, but not in those who never drank.

D. Exogenous use of estrogens and progestins

The role of exogenous female hormones in the development of breast cancer remains uncertain, though most reports of the use of combined estrogen and progesterone formulations after menopause report an increased risk of breast cancer. The use of estrogen alone after menopause, which is only safe among women who have undergone hysterectomy (for estrogen alone use increases the risk of endometrial cancer), does not appear to increase a woman's risk of developing breast cancer (21).

Findings regarding birth control pill (BCP) use and breast cancer risk are mixed, but the bulk of evidence suggests that BCPs increase risk during active use, which decreases over time once BCP use is stopped (22). Many have believed that the mixed findings regarding BCPs and breast cancer risk are related to the BCP dose, suggesting that higher doses of estrogens and progestins are more likely to increase breast cancer risk. Higher doses of female hormones were more commonly present in BCPs that were prescribed in the past than in BCPs in current use. However, a recent study which followed 1.8 million women in Denmark who

used contemporary hormonal contraceptives demonstrated that BCPs and IUDs which release progestins increased a woman's risk of breast cancer on average by 20%. Different hormonal formulations did not appear to significantly alter the increase in risk (23).

E. Ionizing radiation

Most cancers can be induced by ionizing radiation, with a linear dose-response noted for most solid cancers (24). As there is generally a time lag of five or more years between exposure and the development of radiation induced cancer, many of the most revealing studies have been performed in children and young adults who received radiation for the diagnosis and treatment of cancer. The most radiosensitive organ sites in children, in order of sensitivity, are the thyroid gland, breasts, bone marrow, brain and skin (25). At one time, infants received radiation to treat certain benign lesions (hemangioma and an enlarged thymus). Infants who received on average 30 cGy to treat an hemangioma had a 40% increased risk of breast cancer while those who received 70 cGy to treat an enlarged thymus had a 250% excess risk of developing breast cancer (25). The excess risk persisted for up to 50 years after the radiation exposure.

Studies of radiation exposure from multiple chest X-rays used to monitor treatment for tuberculosis (TB) in adolescent girls and young women and a study of multiple X-ray examinations to monitor curvature of the spine in girls with scoliosis have reported increased mortality from breast cancer with increasing radiation dose, with the increased breast cancer risk appearing 15 years after radiation exposure and the risk remaining elevated up to 50 years later (24).

Young women who receive computerized tomography (CT) scans of the chest or heart may also be at increased breast cancer risk. The records of almost a quarter of a million women, who underwent imaging between 2000 and 2010, were reviewed and breast cancer risk determined. Those who underwent CT or nuclear medicine scans which exposed breast tissue to radiation were compared to National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) breast cancer risk data (control). The authors concluded that a child or young adult under the age of 23 who received two or more chest or cardiac CTs had more than double the normal 10 year risk of developing breast cancer (26).

Therapeutic radiation to treat a childhood cancer is also associated with increased breast cancer risk. An assessment of 1,230 female childhood cancer survivors treated with chest irradiation demonstrated that by age 50 years the incidence of breast cancer was 30% overall, and 35% among those receiving radiation to treat Hodgkin's lymphoma (27). This is compared to a lifetime breast cancer risk of 12.4% in otherwise healthy women (28).

F. Pregnancy and nursing

Immediately following childbirth there is an increased risk of breast cancer observed for women of all age groups. Over the long term, parity is protective for women whose first full term pregnancy (FFTP) was completed at a young age (<26), and increased in parous women whose FFTP occurred after 35 years of age (29). Breast cancer diagnosed shortly after childbirth tends to be aggressive. It is more likely to be hormone-insensitive, higher grade, with a higher proliferative rate (30) and a higher likelihood of bone marrow metastases (31).

Observational studies have demonstrated inconsistent findings regarding nursing, length of nursing and risk of premenopausal breast cancer. A prospective cohort study, part of the Nurses' Health Study II, involving 60,075 women demonstrated an inverse association (HR=0.75) between having ever breastfed and risk of premenopausal breast cancer (32). There was no association between length of lactation and risk. Subset analysis demonstrated that the influence of lactation on premenopausal breast cancer risk was limited to women at increased breast cancer risk because of a first degree relative who had developed breast cancer (HR=0.41). There was no association between lactation and breast cancer risk among women of normal risk.

2. Chemoprevention

A. Overview

Two selective estrogen receptor modular (SERM) medications, tamoxifen and raloxifene, are approved by the FDA to prevent breast cancer in high risk women. In the studies which helped support FDA approval, high risk was defined as women 60 years or older, 5-year risk of invasive breast cancer ≥1.67% or lifetime breast cancer risk of at least 20% of developing invasive breast cancer based on the BCRAT (7). SERMs act as an anti-estrogen in some organ systems, and in a pro-estrogenic fashion in others. Tamoxifen was the first agent to be approved, and the only one approved for use in both pre- and post-menopausal women. The Breast Cancer Prevention Trial, started in 1992 and funded by the U.S. National Cancer Institute, enrolled 13,388 pre- and post-menopausal women deemed to be at increased breast cancer risk. Approximately equal numbers of women received tamoxifen or placebo. Tamoxifen reduced the risk of invasive breast cancer by 49% overall and in all age subgroups by over 40% (33). It also reduced the incidence of ductal carcinoma *in situ* (DCIS) by 50%, lobular carcinoma in situ (LCIS) by 56% and atypical hyperplasia by 86%. Tamoxifen also reduced the number of hip, radius and spine fractures. On the other hand, there was an increased risk of developing endometrial cancer, stroke, pulmonary embolism, and deep vein thrombosis. The risk of developing one or more of these side effects was higher in women over age 50. The International Breast Cancer Intervention Study (IBIS)-I clinical trial based in Europe, used the Tyrer-Cuzick risk assessment tool and required that women have a 10 year risk of developing breast cancer of at least 5% (7). The study enrolled 7.154 pre- and post-menopausal women deemed to be at increased risk of developing breast cancer. They were randomized to tamoxifen or placebo. Long term follow-up (median 16 years) demonstrated that tamoxifen decreased the risk of breast cancer (HR=0.71) overall, estrogen receptor (ER) positive invasive breast cancer (HR=0.66) and DCIS (HR=0.65), but not invasive ER negative breast cancer (34).

Raloxifene was approved based in part on findings from a prospective, randomized trial that by compared the agent to tamoxifen. At the time the trial started, raloxifene was already FDA approved to treat osteoporosis in postmenopausal women. Therefore, the trial comparing raloxifene to tamoxifen enrolled only postmenopausal women. Among the 19,747 women enrolled, median age was 58.5 years. The risk of developing invasive breast cancer was similar between the two agents, though there were 40% fewer cases of DCIS in the tamoxifen group (35). There was a 38% lower incidence of uterine cancers (HR=0.62), thromboembolic events (HR=0.70) and cataracts (HR=0.79) in the raloxifene group.

In 2013 the American Society of Clinical Oncology issued and updated guideline on interventions to reduce the risk of breast cancer in women at increased risk for the disease. The guideline was the third addressing the use of chemopreventive medications in women at increased breast cancer risk, and the first to recommend discussing

the option of exemestane, an aromatase inhibitor, as an alternate to tamoxifen or raloxifene in postmenopausal high risk women (36). In the MAP.3 trial, exemestane was compared with placebo or celecoxib plus exemestane in 4.560 postmenopausal women deemed to be at increased breast cancer risk (37). Exemestane (plus or minus celecoxib) decreased the risk of ER positive (HR=0.27) but not ER negative (HR=0.80, but p>0.05) invasive breast cancer. DCIS incidence was lower with exemestane (HR=0.65), but the difference did not reach statistical significance. The IBIS II trial recruited postmenopausal women from 18 countries in a prospective randomized study comparing another aromatase inhibitor, anastrozole, vs. placebo. After a median follow-up of 5 years, anastrozole decreased the risk of developing breast cancer (HR=0.47) (38).

B. Specific subgroups: histopathologic alterations and breast density findings which increase risk

There are many benign breast disease alterations identified on needle or excisional breast biopsy which have been associated with increased breast cancer risk. In general, these alterations can be separated into hyperplasia (usual or atypical) and LCIS. The risk of developing breast cancer in women with usual hyperplasia is increased 50-100%, whereas atypical hyperplasia of the breast increases risk 4-5 fold (39), or 1.5-2% per year (40). The risk of breast cancer development in patients with LCIS is 2% per year, compared to the risk in otherwise healthy women of < 0.4% per year (41). Women with atypical hyperplasia or LCIS have a greater than 30% lifetime risk of developing breast cancer (42). There are few indicators in these high-risk women which assist the treating healthcare provider in determining if the patient will develop invasive breast cancer, with the possible exception of the extent of disease. Greater disease extent increases risk both for women diagnosed with atypical hyperplasia (43) and LCIS (41). The lack of clarity regarding which individuals with atypical hyperplasia and LCIS will go on to develop breast cancer is a problem when counseling women regarding risk reduction, since chemoprevention and surgical strategies have the potential for side effects. Moreover, while bilateral mastectomy is an option for those with LCIS, it is not generally recommended when one is diagnosed with atypical hyperplasia.

Women with dense breasts on mammogram have an increased risk of developing breast cancer, and increased density makes breast cancer detection when reading two dimensional mammograms more difficult (44). However, it is not clear if reducing MBD reduces risk. The chemopreventive agent tamoxifen was evaluated for its potential ability to reduce MBD in women at increased breast cancer risk. MBD measurements were obtained before starting tamoxifen or placebo and on treatment at 12- to 18-month intervals. A reduction in MBD was noted within 18 months of tamoxifen treatment, which lasted for at least 54 months. After 54 months on tamoxifen, MBD decreased on average 13.4% in women 45 years or younger at entry vs. 1.1% in women over 55 years at entry (45). it is not clear that this risk reduction is due to tamoxifen's effect on MBD, on other breast cancer risk factors, or both (44). It appears that the influence of MBD on breast cancer risk is primarily in women with non-proliferative breast disease, with little influence on future risk among women with atypical hyperplasia (46).

3. Surgical approaches to breast cancer prevention: mastectomy and/or oophorectomy

Among the breast cancer driver genetic mutations that have been identified, including *BRCA 1* and *2, TP53, PTEN, STK11, CDH1, PALB2, CHECK2, ATM, NBN,* and *NF1* (8), each alteration imparts its own unique implications regarding future breast cancer risk. Guidelines as to which therapies are reasonable are based on known risk implications. Guidelines are updated from time to time based on the latest available information. Current recommendations from the American Society of Breast Surgeons is that risk reducing bilateral mastectomy is a reasonable approach for women without breast cancer who have a known deleterious mutation in *BRCA 1, BRCA2, TP53, PALB2, CDH1,* or *PTEN*. Risk-reducing mastectomy is recommended for consideration for patients with deleterious mutations in *CHEK2* or *ATM* if the patient has a family member with breast cancer (8). Increased surveillance with breast MRI and mammogram, but not bilateral risk-reducing mastectomy, is recommended for patients with mutations in *STK11, NF1,* and *NBN*. Screening is recommended to start at age 30 for *STK11* and *NF1*, and at age 40 for *NBN* (8).

Bilateral risk-reducing mastectomy is also recommended for consideration in women with a history of prior therapeutic mantle radiation (47) and with a diagnosis of LCIS. An additional option for risk reduction in those diagnosed with LCIS is chemoprevention, as tamoxifen was shown to decrease the risk developing breast cancer in this population of women (33). Mastectomy is not recommended as a routine procedure for risk reduction in the contralateral breast of women diagnosed with cancer in the ipsilateral breast, but may be discussed with the patient based on individual risks and benefits, such as a strong family history and a known deleterious genetic mutation which increases breast cancer risk (48). Alternatives include chemoprevention, which reduces the risk of contralateral breast cancer in women diagnosed with cancer in the ipsilateral breast, including women demonstrated to carry a deleterious *BRCA1* or *BRCA2* mutation (49).

Bilateral salpingo-oophorectomy (BSO) can be considered for risk reduction in genetically high-risk women. BSO reduces breast cancer risk in premenopausal *BRCA 1* and *2* mutation carriers by approximately 50%, similar to tamoxifen, compared to a 90% reduction in similar women who undergo bilateral mastectomy (50). BSO also reduces the risk of ovarian cancer in these women by 90% (51).

The Future of Breast Cancer Prevention

Innovations have greatly advanced our understanding of breast cancer. These innovations have driven a precision based, patient focused approach to the treatment of breast cancer. These same and similar innovations are driving the future of breast cancer prevention.

1. Precision medicine

The ability to sequence a patient's entire genome from a blood or tissue sample has dramatically improved in recent years. Multiple companies and cancer centers now offer whole genome sequencing of a patient's tumor to identify targetable mutations for treatment, and increasingly treatment trials are being designed based on a given genetic alteration rather than on the site of tumor origin. The NCI has launched a clinical trial called NCI-Match, in which patients are assigned treatment based on the genetic changes found in their tumors rather than on disease site (52). The origin of cancer can be from a variety of tumor sites, including the breast. Gene sequencing laboratories that are participating in the study including Foundation Medicine, Caris Life Sciences, MD Anderson Cancer Center, and Memorial Sloan-Kettering Cancer Center.

Studies have been reported in a variety of cancers addressing how gene alterations may guide chemopreventive strategies. For example, EGFR mutations have been identified in the histologically normal epithelium of patients with lung cancer, and PI3K/AKT activation has been identi-

fied in the airways of smokers with precancerous lesions (53). A cancer prevention trial using myo-inositol in patients with bronchial dysplasia demonstrated significant reductions in the inflammatory cytokine IL-6, though other cancer-associated biomarkers did not significantly change with treatment. Among participants with a complete response in the myo-inositol arm, there was a significant decrease in a gene expression signature reflective of PI3K activation (p=0.002) (54). Investigators of the study suggest that a more detailed assessment of molecular alterations in the bronchial tissue may identify additional alterations which could be targeted and hopefully increase the efficacy of myo-inositol as a chemopreventive agent. Future studies which emphasize molecular approaches to breast cancer chemoprevention are likely.

The NCI has issued a request for applications (RFA) for Pre-Cancer Atlas Research Centers (RFA –CA-17-035) (55). This call is a companion to CA-17-034, Human Tumor Atlas Research Centers. In the pre-cancer atlas RFA, the NCI is looking for proposals that focus on a multidimensional cellular, morphological and molecular mapping of human pre-malignant tumors, complemented with critical spatial information (at the cellular and/or molecular level) that facilitates visualization of the structure, composition, and multiscale interactions within the tumor ecosystem over time resulting in tumor progression or regression. The RFA posits that a deeper understanding of the transition from the pre-malignant to the malignant state as a function of time will allow the development of more precise risk stratification methods and effective early intervention strategies.

2. Immunoprevention

The immunoprevention of cancer has been in place for some time with the use of cancer vaccines. A vaccine to the hepatitis B virus produced an 80% reduction in the development of hepatocellular cancer in Taiwan (56). A three-dose prophylactic vaccine to human papilloma virus (HPV) is 90-100% effective in preventing HPV infection and associated anogenital malignancies (53). Fewer doses may be as effective as the three-dose regimen.

Vaccines to prevent non-viral induced cancers is an attractive approach to cancer prevention. A validation study is underway targeting MUC1 for the primary prevention of colon cancer based on initially promising results (57). Preliminary results evaluating a HER2 vaccine for the prevention of recurrence in women with a history of HER2 positive breast cancer were also encouraging (58). Vaccines which induce immunity to multiple antigens are in development as well, and may be more effective than single agent vaccines in activating the immune system to target premalignant lesions of the breast (59).

3. Tumor microenvironment (TME)

The TME appears to be altered early on in the development of cancer (53). The microenvironment becomes immunosuppressive such that immunoprevention strategies are less effective. Checkpoint inhibitors (targeting CTLA-4, PD-1, PD-L1 and PD-L2), have been effective in decrease the immunosuppressive TME when cancer is present. These agents are rather toxic, however, and therefore other strategies, such as depleting suppressive T cells (Tregs), may be better (53) for enhancing vaccine and other immunoprevention strategies.

4. Targeting specific populations

Cancer prevention currently targets high risk individuals, based on known risk factors such as evidence of a deleterious mutation in a breast cancer oncogene (e.g. *BRCA1* and *2*), family history, and breast biopsy premalignant changes. A high-risk population that has been targeted to a lesser degree are individuals who are obese. This is starting to change. The NCI is funding a study to determine if metformin, an FDA approved medication for the treatment of diabetes which has shown preliminary promise as a cancer preventive agent, will decrease the risk of obesity related postmenopausal breast cancer (NIH grant no. R01CA172444-05).

5. Single vs. multiple agents

Demonstration and validation of the safety and efficacy of a single agent, or at least preclinical evidence for synergy among two or more agents with evidence of clinical safety, is generally a pre-requisite to the initiation of a multiple agent clinical study. It is therefore perhaps not surprising that the vast majority of chemoprevention clinical trials conducted thus far have evaluated single agents. Cancer treatment is generally more effective when targeting multiple driver pathways with multiple agents, as opposed to only one. It is likely that this is also true for precancers. Findings from a lung cancer prevention trial involving the administration of myo-inositol vs. placebo in smokers with bronchial dysplasia demonstrated an effect on the targeted PI3K/Akt pathway, but limited to no effect on other affected pathways, leading to no overall improvement in response with active agent vs. placebo (54). A recent randomized clinical trial showed increased efficacy of combination chemoprevention in patients with familial adenomatous polyposis which targeted two pathways, Wnt/EGFR and COX, using sulindac and erlotinib vs. either agent alone (60).

6. Increasing the use of agents proven effective in preventing breast cancer

As previously mentioned, there are two agents (tamoxifen and raloxifene) currently approved for the prevention of breast cancer in postmenopausal high-risk women. Two aromatase inhibitors, exemestane and anastrozole, also demonstrate promise in preventing breast cancer in this population. Tamoxifen is also FDA approved for the prevention of breast cancer in premenopausal high-risk women. The percentage of eligible women taking a chemoprevention medication to decrease their risk of breast cancer is less than 10% (61). There are a variety of reasons for this. For many women, consideration of chemoprevention is not discussed with them by a healthcare provider (62). Moreover, many are concerned about the potential side effects such as endometrial cancer and blood clots with tamoxifen, others stop the medication because they have experienced a side effect, most commonly hot flashes. Indeed, for individuals who initiate a medication, the most common reason to stop is due to side effects (63). Women less likely to take chemoprevention are older, smokers and those with depression (62).

How to overcome this? There are newer SERMs (arzoxifene, bazedoxifene and lasofoxifene) with evidence of efficacy with a lower risk of side effects than tamoxifen (64). Lowering the dose or intermittent dosing of tamoxifen appears to decrease side effects while maintaining biologic efficacy (7). In a short term pre-surgical window trial, transdermal 4-hydroxytamoxifen applied directly to the breast skin showed promising preliminary evidence of efficacy comparable to oral tamoxifen (65). Transdermal delivery appeared to reduce the systemic effects on endocrine and coagulation parameters, though the incidence of hot flashes was similar in both groups.

Summary

We are already aware of important risk factors that lead to cancer (smoking, obesity, lack of exercise, high alcohol intake) which are being addressed, with some success. To increase our impact on cancers that are caused by these behaviors, we need to overcome the inertia at

a personal and social level with regard to adopting healthy behaviors. Equally important, we need to encourage activities such as breastfeeding that are associated with lower risk of breast cancer, at least among women with a family history of the disease. We need to continue to educate clinicians on the hazards of ionizing radiation, and the adoption of imaging approaches which mitigate this.

Vaccines which prevent cancer must continue to be promoted, and new preventive vaccines developed. We should encourage more women with pathologically precancerous lesions and who are genetically at high risk to consider cancer prevention strategies. This requires that we educate their healthcare providers. It also requires that our interventions be safe, easy to use and with limited side effects.

We need to develop new technologies to better identify women at the greatest risk of developing breast cancer. Atypical hyperplasia places women at significantly increased risk, but we lack clear evidence of which women with this diagnosis will have their disease progress to invasive breast cancer. Surgical risk reduction is currently not recommended for most women who are at increased risk and chemoprevention uptake is not used by most women due to the risk of side effects. We need to develop tools that can better predict which women are at the greatest risk of developing breast cancer so that healthcare providers can better counsel them, and that women can better weigh the risks and benefits of active intervention, such as chemoprevention, vs. observation.

Risk assessment needs to be personalized. There have been many paradigm-changing advances in cancer prevention, and many more to come. Developing safe and effective agents, personalizing preventive therapy, and harnessing technology will be increasingly important in getting public buy-in and achieving greater participation in cancer prevention trials.

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