Chemoprevention: Achievements and Future Perspectives

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ABSTRACT: Cancer is the second deadliest disease in the world with very high potential of prevention. The past few decades have witnessed an increased interest in cancer chemoprevention among researchers, clinicians and the public because a successful prevention strategy could save millions of lives. This new paradigm has led to the critical evaluation of prospective chemopreventive agents including natural dietary agents, molecular targeted agents, vaccines etc. preclinically and clinically. Many dietary agents were accorded chemopreventive status based on epidemiological studies that linked their consumption to reduce cancer risk. Despite demonstrated effectiveness in preclinical and animal model studies, their safety with long-term use remains a major concern. Although more rigorous clinical trial protocols have been developed to assess candidates for chemoprevention, accrual, compliance, and retention in chemoprevention trials possess significant challenge because volunteers for such trials are healthy people with high risk of developing cancer. In this review, we critically review various preventive strategies, promising chemopreventive agents, challenges associated with successful chemoprevention and potential ways to overcome these obstacles.

Key words: Chemoprevention, tamoxifen, natural compounds, vaccines

INTRODUCTION

Cancer is a collection of over 100 devastating diseases and is the second leading cause of death worldwide. With an estimated 17.9 million new cancer cases and approximately 10 million cancer deaths in 2020, cancer is set to overtake cardiovascular diseases as the leading cause of death around the world by 2030.[1,2] Not only adversely impacting millions of lives, but cancer is also putting an enormous toll on expenditures and is becoming a growing economic concern for patients and their families, healthcare policymakers, healthcare systems, physicians, employers, and society overall. In 2017, estimated cancer healthcare spending in the USA was $161.2 billion.[3] Unless there are significant breakthroughs in cancer prevention, early diagnosis and treatment, the numbers are projected to rise to 27.5 million new cases and 16.3 million deaths in 2040, and the cost as well.[4] The rise in cancer prevalence could be attributed to an increasingly aging global population, unhealthy feeding habits and poor physical activity.[5,6] Although the current global burden of cancer is higher in developed countries, this pattern is expected to change over the next two decades with changes in the world demography and increased risk factors related to urbanization and the growth of emerging economies.[1] Consequently, the cancer burden in developing countries will likely rise drastically if adequate preventive measures and screening infrastructures are not put in place. In this review, we discuss cancer chemoprevention as a mean to reduce global cancer burden, review various preventive strategies, different classes of promising chemopreventive agents, challenges associated with successful chemoprevention and potential ways to overcome these obstacles.

Cancer: A mostly preventable disease. The lifetime probability of developing cancer is about 40%, slightly higher for men (40.5%) than for women (38.9%).[1] Extensive oncology research has improved our understanding of carcinogenesis and

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has shown that tumorigenesis is a multi-step lengthy process, often takes years to develop into invasive cancer. The long latency periods and involvement of multiple histologic stages and molecular changes (such as gene mutations, amplification, deletion, loss of heterozygosity etc.) provide enormous opportunities for diagnosis and intervention at precancerous stages before they become full-blown cancers (Figure 1). Despite its deadly nature, cancer is mostly a highly preventable disease. About 40% of cancer cases are attributed to preventable risk factors including smoking, excess body weight, alcoholism, poor diet, physical inactivity, and exposure to ultraviolet light and other environmental and biological carcinogens (chemicals and infectious agents).[4] Avoidance of these cancer-causing biological, chemical, and physical agents, and the habitual consumption of diets high in foods rich in antioxidants are important ways to prevent cancer. Approximately, 30% to 40% of cancer incidents are preventable by consuming a healthy diet, regular physical activity and maintenance of optimum body weight, and more than 20% by diets high in vegetables and fruits.[6,7]

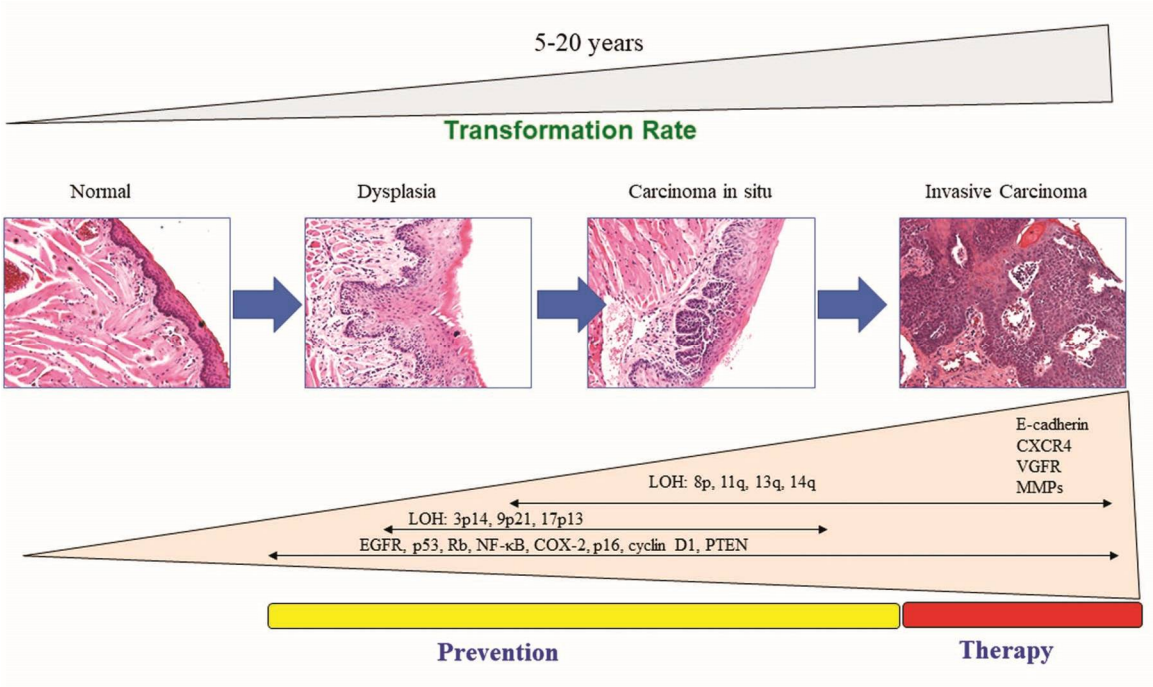

Figure 1. Multistep carcinogenesis process and scopes of chemoprevention. Images represent various histologic changes of normal mouse oral epithelia after exposure to 4-Nitro quinoline (representative images from our unpublished 4-NQO-induced oral carcinogenesis pilot study). Below Images: Molecular changes associated with each step in the oral carcinogenesis process[72]. Yellow bar: Scopes for chemoprevention; Red bar: requires treatment. The upper arrow indicates the initial slow process which speeds up with time. EGFR-Epidermal Growth Factor Receptor; Rb- Retinoblastoma gene; PTEN-Phosphatase and Tensin homolog; NF-κB-nuclear factor κB; LOH-loss of heterozygosity.

Cancer prevention is a means of reducing cancer burden by stopping the development of invasive cancers. Generally, cancer prevention could be classified as primary, secondary or tertiary based on the goals of individual strategies.[8] Primary prevention is the avoidance of cancer development in normal, healthy individuals who are at high risk of tumor development such as smokers, persons with human papillomavirus (HPV) or helicobacter infections, etc. Primary prevention aims to prevent the development of cancer in populations who are at high risk where the carcinogenesis process might be initiated, but no precancerous lesion is detectable. For example, the administration of HPV vaccines to prevent cervical cancer in women and oral cancer in men.[9,10] Secondary prevention is the prevention of cancers in

patients with premalignant conditions, i.e., with visible cellular changes like dysplasia. Secondary prevention includes interventions that detect and curb precancerous processes before it spreads beyond the primary tissue. The goal of secondary prevention is to reverse the precancerous lesions to normal or prevent/slow down the progression of precancerous lesions to invasive cancer. For example, surgical excision of colorectal polyps by colonoscopy[11] or administration of tamoxifen for prevention of breast cancer.[12] Tertiary prevention is the prevention of recurrence or development of a second primary tumor in patients cured of initial cancer. The goal of tertiary prevention is to prevent disease recurrence or the development of a second primary tumor in those individuals who have already endured potentially curative therapy.[13,14] For example maintenance therapy of breast cancer patients with tamoxifen following the initial cure.

There are multiple approaches for cancer prevention:

1) Surgical prevention such as prophylactic surgery or screening and resection of preinvasive neoplasia. The double mastectomy undergone by the actress, Angelina Jolie, after she learned that she carried a defective BRCA1 gene is a perfect example of prophylactic surgery. Removal of colorectal polyps by colonoscopy or resection of oral premalignant lesions are examples of the second type.[15,16]
2) Behavioral prevention approaches such as smoking cessation to prevent smoking-associated cancers[17]; screening and genetic counseling; overweight and obesity control, cancer awareness education (cancer survivors and women health initiative), etc.
3) Biological prevention such as the HPV vaccine to prevent cervical cancer in women and oral cancer in men[10]; and HBV vaccine to prevent liver cancer.[18]
4) Chemoprevention - intervention with synthetic or naturally occurring chemical compounds.

Coined by Michael Sporn in 1976, chemoprevention is defined as a means of cancer control by which the occurrence of the disease can be entirely prevented, slowed down, or reversed by the administration of one or more naturally occurring and/or synthetic agents. That is the goal of chemoprevention is preventing end-stage, invasive disease and impeding or delaying the development of cancer using drugs or pharmacological agents.[19] The distinction between cancer chemoprevention and cancer prevention is that the latter includes other modes of intervention such as surgery, smoking cessation, etc. Chemoprevention is a cost-effective alternative to cancer treatment that could save millions of lives and billions of dollars because chemopreventive interventions are designed to intervene before the development of invasive cancers with safe, cost-effective, easily accessible and orally bioavailable natural or synthetic compounds. The promise of chemoprevention is the significant savings compared to conventional cancer treatments and this has increased its popularity and acceptance.[19,20]

Classes of chemopreventive agents. An ideal chemopreventive agent should be non-toxic to the human body, effective at low doses, readily available and inexpensive, orally active and preferably able to modulate multiple molecular targets.[19] At a particular dose and duration of treatment, it should have a evident mechanism assessable by biological markers to confirm its benefit to at-risk patients.[21] To ensure prevention, the ideal agent should interact with specific targets or dysregulated pathways involved in carcinogenesis. Estrogen receptor signaling, retinoid receptor signaling, EGFR and COX-2 overexpression, androgen signaling, and aromatase activity are some of the pathways and genomic aberrations being studied as potential targets for chemoprevention.[21]

Natural compounds. Many studies have proven that maintaining a healthy diet rich in fruits and vegetables significantly decreases the risk of developing cancers.[22-24] Within these foods are natural compounds that have been identified as being responsible for the tumor-suppressive activity. The beauty of diet-derived natural compounds is their

high margin of safety and their action across multiple molecular targets. For example, green tea, which is enriched with polyphenols like epigallocatechin-3-gallate (EGCG), has been widely studied and reported for its anticarcinogenic activity and remarkable safety profile (up to 1 g of green tea solids can be consumed daily).[19,25] Moreover, it exhibits synergistic activity with erlotinib and tumor necrosis factor receptor apoptosis-inducing ligand (TRAIL).[26, 27] Curcumin is another natural compound with known antitumor potential derived as a pigment from turmeric powder. Since the 1980s, many studies have reported its ability to inhibit the growth of cancer cells *in vitro* and alter carcinogenesis in animal models.[28,29] Like EGCG, curcumin is very safe (up to 8g/day).[30] It also exhibits synergy with anticancer drugs like fluorouracil, vinca alkaloids and gemcitabine[31-33], and increased chemopreventive effects in combination with other dietary polyphenols, for example, green tea, genistein, and embelin.[34-36] These properties have inspired phase I/II clinical trials to study the efficacy, safety, and pharmacokinetic profile of curcumin (Table 1).[30,37,38] However, a major challenge to curcumin's application is its poor oral bioavailability, which has fostered new research into synthetic analogs of curcumin that maintain its anticancer activity and safety profile with enhanced pharmacokinetic properties.[39]

Resveratrol is a phytoalexin known for its cardioprotective and chemopreventive properties. It is abundant in red wines and grapefruit skins and can be consumed safely up to 5 g/day.[40] Several preclinical studies have reported its effectiveness as a chemopreventive agent in both *in vitro* and *in vivo* settings.[41,42] Lycopene is a natural antioxidant present in red tomatoes and processed tomato products. Many studies have reported its ability to decrease the progression of benign prostatic hyperplasia and the development of prostate cancer.[43,44] Luteolin is a flavonoid naturally found in green vegetables. Preclinical studies have shown its ability to induce anticancer effects at several anatomic sites such as the aerodigestive tract, the colon and liver.[45-47] Clinical studies are needed to validate its efficacy in humans.[19] Genistein, found naturally in soybeans, is another natural product with reported anticancer efficacy. The consumption of soybeans was shown to decrease the risk of prostate, breast and endometrial cancer.[48-50] Some clinical studies have shown genistein's efficacy in prostate cancer therapy and tertiary prevention.[51] A recent review article updates these natural agents and discusses new potential natural compounds that exhibit chemopreventive activity *in vitro* and *in vivo*.[25]

Vaccines. Previously, there were theories suggesting that cancers were infectious, but with increased knowledge of cancer biology, these theories have been largely debunked. However, about 2 million cancer cases yearly have confirmed links with infectious agents. Some of the cancers in this category include cervical cancers, oropharyngeal squamous cell carcinoma, and some liver and gastric tumors.[52] HPV infection is the chief causative agent for cervical cancer and HPV vaccines were developed and approved as primary prevention for cervical cancer. These vaccines are effective against different strains of the HPV virus including HPV strains (6, 11, 16, 18, 31, 33, 45, 52, and 58)[53] in adolescent girls. Although not approved yet, the Center for Disease Prevention and Control (CDC) also recommends HPV vaccination for adolescent boys. *H. pylori* infections has been associated with an increased risk of gastric cancers based upon observations that *H. pylori* eradication with antibiotics reduced gastric cancer incidence by 39%.[54] However, antibiotic resistance is a major challenge, but new studies are looking into vaccine-based prevention with reported efficacy in children. The results of a randomized control trial that explored the efficacy of an oral recombinant *H pylori* vaccine reported a 72% vaccine efficacy over the placebo group.[55] The current status of vaccine research and development for *H. pylori* has been reviewed.[56] Hepatitis B Virus (HBV) chronic infection contributes to a high risk of hepatocellular carcinoma or liver cancer. In the 1980s, HBV vaccination was introduced as part of the immunization regimen in most countries around the world. Subsequently, clinical trials conducted in

Africa and China have reported the potential of HBV vaccines to protect against primary liver cancers after 20 years of follow-up. However, because most liver cancers develop in middle age (40s & 50s), these participants are still being observed to ascertain the long-term protective effects of the HBV vaccine against liver cancers.[57,58]

Table 1. Information about cancer chemoprevention clinical trials.

Cancer type and trial No.	Phase	Trial type	Status	Intervention	URL
Skin					
NCT04091022	II	Interventional	Recruiting	Drug: Solaraze and Vaniqa	https://ClinicalTrials.gov/show/NCT04091022
NCT02636569	N/A	Interventional	Active, not recruiting	Drug: topical diclofenac daily|Drug: placebo	https://ClinicalTrials.gov/show/NCT02636569
NCT02347813	II	Interventional	Completed	Drug: Pioglitazone	https://ClinicalTrials.gov/show/NCT02347813
NCT00847912	IV	Interventional	Completed	Drug: 5-fluorouracil| Drug: Placebo, vehicle control	https://ClinicalTrials.gov/show/NCT00847912
NCT00644384	N/A	Interventional	Completed	Drug: acitretin|Genetic: gene expression analysis|Genetic: northern blotting| Genetic: polymerase chain reaction|Genetic: protein expression analysis|Other: laboratory biomarker analysis	https://ClinicalTrials.gov/show/NCT00644384
NCT00204789	II	Interventional	Completed	Drug: Difluoromethylornithine	https://ClinicalTrials.gov/show/NCT00204789
NCT00005884	III	Interventional	Completed	Drug: eflornithine	https://ClinicalTrials.gov/show/NCT00005884
NCT00006219	II	Interventional	Completed	Drug: clarithromycin|Drug: prasterone	https://ClinicalTrials.gov/show/NCT00006219
NCT00003611	N/A	Interventional	Completed	Drug: acitretin|Other: placebo	https://ClinicalTrials.gov/show/NCT00003611
NCT00007631	III	Interventional	Completed	Drug: Tretinoin 0.1% cream or placebo|Other: Placebo	https://ClinicalTrials.gov/show/NCT00007631
Breast					
NCT04496739	N/A	Interventional	Recruiting	Behavioral: Cancer Educational Materials| Other: Decision Aid| Other: Interview|Other: Questionnaire Administration	https://ClinicalTrials.gov/show/NCT04496739
NCT04359420	N/A	Interventional	Active, not recruiting	Other: BC-Predict|Other: NHS Breast Screening Programme	https://ClinicalTrials.gov/show/NCT04359420
NCT03629717	I	Interventional	Completed	Procedure: Ultrasound-guided core needle biopsy|Drug: Denosumab|Procedure: Blood draw|Drug: Calcium|Drug: Vitamin D	https://ClinicalTrials.gov/show/NCT03629717

NCT03069742	N/A	Interventional	Active, not recruiting	Other: RealRisks|Other: BNAV	https://ClinicalTrials.gov/show/NCT03069742
NCT02954900	N/A	Interventional	Completed	Other: RealRisks|Other: BNAV	https://ClinicalTrials.gov/show/NCT02954900
NCT01905046	III	Interventional	Recruiting	Drug: metformin hydrochloride|Other: placebo	https://ClinicalTrials.gov/show/NCT01905046
NCT01399359		Observational	Completed	Behavioral: Counseling session|Other: Questionnaire 1|Other: Questionnaire 2|Other: online questionnaire	https://ClinicalTrials.gov/show/NCT01399359
NCT01372644	I	Interventional	Completed	Drug: SOM 230 / Pasireotide	https://ClinicalTrials.gov/show/NCT01372644
NCT01166763	N/A	Interventional	Completed	Drug: vitamin D3	https://ClinicalTrials.gov/show/NCT01166763
NCT00859651	II	Interventional	Completed	Drug: Cholecalciferol| Drug: Placebo capsule	https://ClinicalTrials.gov/show/NCT00859651
NCT00295100	II	Interventional	Completed	Drug: Tamoxifen	https://ClinicalTrials.gov/show/NCT00295100
NCT00291694	II	Interventional	Completed	Drug: celecoxib|Other: placebo	https://ClinicalTrials.gov/show/NCT00291694
NCT00291135	II	Interventional	Completed	Drug: letrozole	https://ClinicalTrials.gov/show/NCT00291135
NCT00291122		Observational	Completed	Drug: celecoxib 400 mg BID	https://ClinicalTrials.gov/show/NCT00291122
NCT00291109		Observational	Completed	Drug: letrozole 2.5 mg	https://ClinicalTrials.gov/show/NCT00291109
NCT00291083		Observational	Completed		https://ClinicalTrials.gov/show/NCT00291083
NCT00200174	N/A	Interventional	Completed	Drug: Raloxifene followed by combination therapy|Drug: Exemestane followed by combination therapy	https://ClinicalTrials.gov/show/NCT00200174
NCT00098800	N/A	Interventional	Completed	Drug: fenretinide	https://ClinicalTrials.gov/show/NCT00098800
NCT00003099	II	Interventional	Completed	Drug: Fenretinide|Drug: Tamoxifen Citrate|Other: Placebo	https://ClinicalTrials.gov/show/NCT00003099
NCT00078832	III	Interventional	Active, not recruiting	Drug: anastrozole|Drug: placebo	https://ClinicalTrials.gov/show/NCT00078832
NCT00073073	II	Interventional	Completed	Drug: Exemestane| Dietary Supplement: Calcium carbonate| Dietary Supplement: Vitamin D	https://ClinicalTrials.gov/show/NCT00073073
Bladder					
NCT00729287	III	Interventional	Completed	Dietary Supplement: selenium|Other: placebo	https://ClinicalTrials.gov/show/NCT00729287
NCT00003623	III	Interventional	Completed	Dietary Supplement: multivitamin|Other: Placebo	https://ClinicalTrials.gov/show/NCT00003623
NCT00006124	II|III	Interventional	Completed	Drug: celecoxib|Drug: placebo	https://ClinicalTrials.gov/show/NCT00006124
NCT00004154	III	Interventional	Completed	Drug: Fenretinide|Other: Placebo	https://ClinicalTrials.gov/show/NCT00004154
Lung					
NCT03598309	II	Interventional	Recruiting	Drug: Curcumin C3 complexÂ®|Drug: LovazaÂ®|Other: Placebo	https://ClinicalTrials.gov/show/NCT03598309

NCT03232138	II	Interventional	Recruiting	Dietary Supplement: Sulforaphane|Drug: Placebo	https://ClinicalTrials.gov/show/NCT03232138
NCT02719860	II	Interventional	Completed	Dietary Supplement: Green tea|Dietary Supplement: Black tea|Dietary Supplement: Placebo tea	https://ClinicalTrials.gov/show/NCT02719860
NCT00780234	II	Interventional	Completed	Procedure: fluorescence bronchoscopy|Procedure: quantitative high resolution CT scan|Drug: PIOGLITAZONE VS. PLACEBO 30 mg	https://ClinicalTrials.gov/show/NCT00780234
NCT00363805	II	Interventional	Completed	Dietary Supplement: green tea|Drug: Polyphenon E|Other: placebo	https://ClinicalTrials.gov/show/NCT00363805
NCT00175747	II|III	Interventional	Completed	Drug: Inhaled Budesonide 800 Âµg twice daily	https://ClinicalTrials.gov/show/NCT00175747
NCT00084409	II	Interventional	Completed	Drug: iloprost|Other: placebo	https://ClinicalTrials.gov/show/NCT00084409
NCT00055978	II	Interventional	Completed	Drug: celecoxib|Other: placebo	https://ClinicalTrials.gov/show/NCT00055978
NCT00020878	II	Interventional	Completed	Drug: celecoxib	https://ClinicalTrials.gov/show/NCT00020878
NCT00008385	III	Interventional	Completed	Other: placebo|Drug: selenium	
HNSCC					
NCT02608736	Early I	Interventional	Completed	Drug: Valproic Acid|Drug: Placebo	https://ClinicalTrials.gov/show/NCT02608736
NCT01192204	I|II	Interventional	Completed	Drug: 10% FBR containing bioadhesive gel|Drug: placebo gel	https://ClinicalTrials.gov/show/NCT01192204
NCT01116336	I	Interventional	Completed	Drug: Erlotinib|Dietary Supplement: Green Tea Polyphenon E	https://ClinicalTrials.gov/show/NCT01116336
NCT00570232	II	Interventional	Completed	Drug: Erlotinib	https://ClinicalTrials.gov/show/NCT00570232
NCT00299195	N/A	Interventional	Completed	Drug: sulindac|Drug: Placebo	https://ClinicalTrials.gov/show/NCT00299195
NCT00201279	III	Interventional	Completed	Drug: 13-cis Retino Acid	https://ClinicalTrials.gov/show/NCT00201279
Colon					
NCT02647671	I	Interventional	Completed	Drug: AquaminÂ®| Drug: Calcium Carbonate|Drug: Placebo	https://ClinicalTrials.gov/show/NCT02647671
NCT00468910	II	Interventional	Completed	Drug: acetylsalicylic acid|Drug: placebo|Other: laboratory biomarker analysis	https://ClinicalTrials.gov/show/NCT00468910
NCT00018551	II	Interventional	Completed	Drug: Folic Acid	https://ClinicalTrials.gov/show/NCT00018551
Colorectal					
NCT02965703	II	Interventional	Recruiting	Drug: Aspirin|Other: Laboratory Biomarker Analysis|Other: Placebo Administration|Other: Questionnaire Administration	https://ClinicalTrials.gov/show/NCT02965703

NCT01894685	II	Interventional	Completed	Drug: Mesalazine|Drug: Placebo	https://ClinicalTrials.gov/show/NCT01894685
NCT01574027	II	Interventional	Completed	Drug: Vitamin D3 (cholecalciferol)|Drug: Placebo	https://ClinicalTrials.gov/show/NCT01574027
NCT01333917	I	Interventional	Completed	Drug: Curcumin C3 tablet	https://ClinicalTrials.gov/show/NCT01333917
NCT00002527	III	Interventional	Completed	Drug: aspirin|Other: placebo	https://ClinicalTrials.gov/show/NCT00002527
NCT00002650	II	Interventional	Completed	Dietary Supplement: folic acid	https://ClinicalTrials.gov/show/NCT00002650
NCT00033371	II	Interventional	Completed	Drug: Celecoxib|Other: Placebo|Drug: eflornithine|Other: Laboratory biomarker analysis|Other: Questionnaire administration	https://ClinicalTrials.gov/show/NCT00033371
NCT00001693	I	Interventional	Completed	Drug: Celecoxib (SC-58635)	https://ClinicalTrials.gov/show/NCT00001693
Esophageal					
NCT01447927	II	Interventional	Completed	Drug: metformin hydrochloride|Other: placebo	https://ClinicalTrials.gov/show/NCT01447927
NCT00003076	II	Interventional	Completed	Drug: eflornithine	https://ClinicalTrials.gov/show/NCT00003076
NCT00005878	II	Interventional	Completed	Drug: celecoxib	https://ClinicalTrials.gov/show/NCT00005878
Gastric					
NCT02794428	II	Interventional	Recruiting	Drug: Eflornithine|Other: Eflornithine placebo	https://ClinicalTrials.gov/show/NCT02794428
NCT00585637	I	Interventional	Completed	Drug: Vitamin D|Dietary Supplement: Placebo	https://ClinicalTrials.gov/show/NCT00585637
Prostate					
NCT03103152	II|III	Interventional	Completed	Drug: High dose Aspirin & Vitamin D|Drug: High dose Aspirin, Vitamin D placebo|Drug: Low dose Aspirin , Vitamin D|Drug: Low dose Aspirin, Vitamin D placebo|Drug: Aspirin Placebo, Vitamin D|Drug: Aspirin placebo, Vitamin D placebo	https://ClinicalTrials.gov/show/NCT03103152
NCT02423759	IV	Interventional	Completed	Drug: ciprofloxacin|Drug: ciprofloxacin and gentamycine|Drug: culture-based chemoprophylaxis	https://ClinicalTrials.gov/show/NCT02423759
NCT02381015	N/A	Interventional	Completed	Genetic: Genetic Risk Score: Number Format|Genetic: Genetic Risk Score: Number + Pictograph|Behavioral: Family History: Number Format|Behavioral: Family History: Number + Pictograph	https://ClinicalTrials.gov/show/NCT02381015

NCT01265953	N/A	Interventional	Completed	Drug: SFN-rich broccoli sprout extract capsules|Dietary Supplement: Gelatin capsule containing microcrystalline cellulose.	https://ClinicalTrials.gov/show/NCT01265953
NCT00780754	III	Interventional	Completed	Drug: dutasteride|Procedure: prostate biopsy	https://ClinicalTrials.gov/show/NCT00780754
NCT00752739	II	Interventional	Completed	Dietary Supplement: selenium|Other: placebo	https://ClinicalTrials.gov/show/NCT00752739
NCT00446901	N/A	Interventional	Completed	Dietary Supplement: Selenium	https://ClinicalTrials.gov/show/NCT00446901
NCT00270647	N/A	Interventional	Completed	Dietary Supplement: Vitamin E|Dietary Supplement: Vitamin C|Dietary Supplement: Multivitamin|Dietary Supplement: Beta-carotene	https://ClinicalTrials.gov/show/NCT00270647
NCT00006214	II	Interventional	Completed	Drug: flutamide|Other: placebo	https://ClinicalTrials.gov/show/NCT00006214
NCT00030901	III	Interventional	Completed	Drug: L-selenomethionine|Drug: L-selenomethionine placebo	https://ClinicalTrials.gov/show/NCT00030901
NCT00006101	II	Interventional	Completed	Drug: eflornithine|Drug: Placebo	https://ClinicalTrials.gov/show/NCT00006101
NCT00028353	II	Interventional	Completed	Drug: GTX-006 (Acapodene)	https://ClinicalTrials.gov/show/NCT00028353
Precancerous					
NCT00031759	II	Interventional	Completed	Drug: imiquimod|Procedure: Ablative or excisional therapy	https://ClinicalTrials.gov/show/NCT00031759
NCT00036283	II	Interventional	Completed	Drug: Celecoxib	https://ClinicalTrials.gov/show/NCT00036283
NCT00314262	I/II	Interventional	Completed	Drug: Erlotinib & Celecoxib	https://ClinicalTrials.gov/show/NCT00314262

Abbreviations: N/A , Not Applicable

Anti-inflammatory agents. There is overwhelming evidence that inflammation through COX-2 upregulation is a common feature of carcinogenesis. It is not clear if there is a causal relationship between inflammation and carcinogenesis, but the association is very strong.[53] Most carcinogens induce COX-2 mediated prostaglandin synthesis which is an essential feature of premalignant and malignant neoplasm. Therefore, the inhibition of COX-2 mediated inflammation has proven potential in cancer chemoprevention.[59] Both selective and non-selective COX-2 inhibition with non-steroidal anti-inflammatory drugs (NSAIDs) reduced the risk of cancer development but COX2 selective inhibitors were more efficient.[60] However, a major drawback to the regulatory approval of NSAIDs for chemoprevention, especially COX-1 inhibitors, is the increased risk of gastrointestinal or genitourinary ulceration.[61] COX-2 selective inhibitors, especially celecoxib, have been studied extensively in the clinics for their chemopreventive potential (Table 1), but there are concerns that constant use of selective COX-2 inhibitors like celecoxib may increase the risk of cardiovascular disease. A meta-analysis of 72 studies revealed that daily intake of 400 mg celecoxib had no association

with thrombotic cardiovascular risk.[60] More so, recent clinical studies have obtained encouraging results for the potential combination of celecoxib with EGFR inhibitor erlotinib for the prevention of head and neck cancer.[62] Many pro- and anti-inflammatory cytokines have also been studied in the context of chemoprevention with anti-inflammatory agents. For example, in studying the role of NSAIDs in the modulation of pro- and anti-inflammatory cytokines in DMBA-induced lung cancer, etoricoxib was shown to downregulate pro-inflammatory cytokines like IL-1β, TNF-α and IFN-γ while it upregulated the anti-inflammatory cytokine, IL-2.[63]

Anti-hormonal agents. Some cancers are driven by hormonal action. For example, breast and prostate cancers are dependent on estrogen and 5-hydroxytestosterone, respectively. Tamoxifen is an anti-estrogen initially developed as a contraceptive but is now indicated in the treatment of breast cancer. Tamoxifen was also effective at preventing invasive and non-invasive breast cancer in the National Surgical Adjuvant Breast and Bowel Project (NSABP)-initiated the Breast Cancer Prevention Trial (BCPT; P-1) and was approved by the FDA for high-risk premenopausal women for breast cancer chemoprevention.[64] However, some caution is warranted since there were increased cases of endometrial cancer among women taking tamoxifen. Also, due to its non-selective nature, it inhibits the beneficial effects of estrogen on the bone. For these reasons, newer selective estrogen receptor modulators were developed. An example is raloxifene, which has similar efficacy as tamoxifen but a significantly lower risk of uterine malignancy and thromboembolic events. It was also approved by the FDA as a chemopreventive drug for breast cancer.[20,53] Additionally, the inhibition of enzymes involved in hormone metabolism is another strategy for chemoprevention. For instance, aromatase enzyme is essential for estrogen production, and its inhibition by exemestane was effective at preventing breast cancer in high-risk postmenopausal women.[65] The enzyme, 5-alpha reductase, is responsible for converting testosterone to dihydrotestosterone, which is required for prostate development and growth.[66] Finasteride, a 5-alpha reductase inhibitor was assessed in a prostate cancer prevention trial and demonstrated an overall decrease in prostate cancer incidence among healthy men, though there was an increased high-grade prostate cancer risk when compared to placebo.[67] This drawback has limited the acceptance of finasteride as a chemopreventive agent for prostate cancer although it is approved for the treatment of benign prostatic hyperplasia.[68]

Clinical trials for chemoprevention and challenges. A typical chemoprevention clinical trial follows the 'ABCDEs' guiding principle which includes, obtaining an appropriate agent with defined pharmacology, adequate biomarkers, a representative cohort, a robust study design, and definitive endpoints.[21] Phase I trials are aimed at defining the safety and pharmacokinetic profile of the test agent. Phase II trials observe the efficacy of the test agent compared to a placebo or standard of care against clinical biomarkers. Phase I/II usually involves fewer than 100 participants observed for less than a year. On the other hand, phase III trials are aimed at demonstrating the ability of an agent to reduce the incidence of clinically relevant neoplasia.[14] Such studies usually enroll hundreds to thousands of subjects and observe them for years. Apart from the trial phase, the relative risk of cancer development could determine the duration and number of participants enrolled in a trial. To achieve the same power, trials with low-risk patients would usually require many more participants for a longer period of observation, compared to trials with high-risk patients.[21] Because it is quite difficult to define realistic endpoints for prevention trials, most rely on cancer incidence to demonstrate efficacy, and this may take several years. This limitation makes chemoprevention phase III trials very expensive and unattractive to investors. For conventional anti-cancer agents, however, the FDA grants accelerated approval for most agents that demonstrate ability through surrogate endpoints to impact improved survival and quality-of-life of cancer patients.[69] Another major challenge to chemoprevention is patient hesitancy because studies show that the acceptance of chemoprevention is very low.[70] To

improve acceptance, more studies are required to reaffirm the safety and efficacy of chemopreventive agents. Health promotion campaigns could also serve as an opportunity to raise awareness about the advantages of chemoprevention. Table 1 lists some of the successful and unsuccessful chemoprevention clinical trials.

Conclusion and future directions. In summary, our increased knowledge and understanding of carcinogenesis and ways to interrupt it has ushered a new wave of chemoprevention research, but this is just the beginning. Because of the lack of well-characterized, validated surrogate biomarkers, chemoprevention trials use cancer occurrence as the definite endpoint that can take decades to evaluate making patient adherence and compliance highly challenging.[8] Patient dropout from trials is very common. Moreover, chemoprevention trials are usually designed for healthy populations thus patient accrual poses further hurdles to complete trials.[8] Future studies should focus on ways to better identify individuals at high risk of developing cancer and for whom chemoprevention would be beneficial. Additionally, the identification of critical endpoints is a major challenge to clinical trials for chemopreventive agents. More studies are required to identify precancerous biomarkers that could serve as measures to assess the efficacy of chemoprevention. It is also obvious that many agents with proven efficacy are not applied clinically because of their toxicity over long-term use. Some have purported short-term intermittent therapy as a suitable alternative to continuous treatment.[71] Toxicological studies are needed to ascertain the safety implications of long-term use of these chemopreventive agents. Also, health promotion through education of the public about the benefits of cancer prevention and increased awareness about the devastating nature of cancer is crucial for the successful implementation of chemoprevention in common clinical practice.

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