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## Molecular Cancer Prevention: Current Status & Future Directions

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### Abstract

The heterogeneity and complexity of advanced cancers strongly supports the rationale for an enhanced focus on molecular prevention as a priority strategy to reduce the burden of cancer. Molecular prevention encompasses traditional chemopreventive agents as well as vaccinations and therapeutic approaches to cancer-predisposing conditions. Despite challenges to the field, we now have refined insights into cancer etiology and early pathogenesis; successful risk assessment and new risk models; agents with broad preventive efficacy (e.g., aspirin) in common chronic diseases, including cancer; and a successful track record of more than 10 agents approved by the FDA for the treatment of precancerous lesions or cancer risk reduction. The development of molecular preventive agents does not differ significantly from the development of therapies for advanced cancers, yet has unique challenges and special considerations given that it most often involves healthy or asymptomatic individuals. Agents, biomarkers, cohorts, overall design, and endpoints are key determinants of molecular preventive trials, as with therapeutic trials, although distinctions exist for each within the preventive setting. Progress in the development and evolution of molecular preventive agents has been steadier in some organ systems, such as breast and skin, than in others. In order for molecular prevention to be fully realized as an effective strategy, a number of challenges to the field must be addressed. Here we provide a brief overview of the context for and special considerations of molecular prevention along with a discussion of the results of major randomized controlled trials.

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## Introduction

### Premise & Context for Molecular Prevention

Recent data from sequencing cancer genomes highlights the extent of genetic complexity characteristic of invasive, metastatic (advanced) cancers.<sup>1</sup> Genetic heterogeneity exists on multiple levels: within a single tumor (intratumoral heterogeneity), across patients with the same tumor (interpatient heterogeneity), and within (intrametastatic heterogeneity) and between (intermetastatic heterogeneity) metastases of the same patient. Mutations in nearly 140 genes have been identified that contribute to cancer, with more likely to be discovered. Such complexity challenges treatment and limits responses to therapeutics, often resulting in immediate or delayed resistance, as seen with many of the targeted therapeutic approaches used today (e.g., BRAF inhibitors in melanoma). This heterogeneity and complexity of advanced cancers strongly supports the rationale for an enhanced focus on early detection and prevention as priority strategies to reduce the burden of cancer. For further reading on the genetic heterogeneity of cancer, see Vogelstein et al.<sup>1</sup>

Cancer prevention occurs across the entire disease spectrum, from primary to tertiary prevention, and encompasses a number of strategies, including molecular prevention, which can be primary or secondary in nature. Molecular prevention of cancer can be defined as the use of natural or synthetic agents that interrupt the prime drivers, key derangements or the context in which these drivers act and in which the derangements occur, prior to invasion across the basement membrane. Chemoprevention is one form of molecular prevention that was defined by Dr. Michael Sporn in 1976.<sup>2</sup> Chemopreventive agents were traditionally drugs or micronutrients that could block DNA damage. Molecular prevention encompasses these more traditional chemopreventive agents as well as vaccines and therapeutic interventions in those at high-risk of cancer due to microbial or other diseases (e.g., hepatitis C), as all these ultimately operate at the molecular level and all have the potential to reduce precancer or cancer incidence and mortality.

The identification and development of safe and effective molecular preventive agents offers a promising approach towards cancer prevention. We now have refined insights into cancer etiology and early pathogenesis; successful risk models; the promise of agents with broad preventive efficacy (e.g., aspirin) in common chronic diseases, including cancer; and a successful track record of more than 10 agents approved by the FDA for the treatment of precancerous lesions or cancer risk reduction (Table 1). In addition to these agents, there are also a number of interventions targeted to viruses and bacteria associated with various cancers (Table 2) that, while not expressly indicated for cancer prevention and risk reduction at the present time, nevertheless likely represent effective molecular preventive strategies for cancer risk reduction in the setting of an infectious organism. In this review, we provide a brief overview of the context for and special considerations of molecular prevention, as well as a discussion of the results of major randomized controlled trials (RCTs) of molecular

preventive agents by cancer site. Table 3 provides a compendium of phase III (and some phase II) clinical trials by cancer site.

### Considerations of Molecular Prevention as a Strategy

The premise of molecular strategies to prevent cancer is supported by a number of lines of evidence. First, decades of research have revealed many of the mechanisms of carcinogenesis and have shown it to be a multi-step chronic disease process, often occurring over decades, thus allowing for ample time and opportunity to intervene before cancer is diagnosed. Second, RCTs of the adjuvant therapies tamoxifen and raloxifene in the prevention setting have shown these agents to be both effective and safe in significantly reducing the risk of cancer, offering definitive proof of principle of the concept of molecular prevention in cancer,<sup>3</sup> and suggesting that other approved therapeutic agents may also be efficacious when applied before invasion and metastasis. Third, carcinogenesis is initiated by DNA mutation, but ultimately, the development of a cancer is also the result of other important processes, including epigenetic events and changes in the microenvironment of the tumor, offering additional targets and pathways for pharmacologic modulation, beyond the use of drugs and micronutrients that block DNA damage.<sup>4</sup> Finally, and most recently, sequencing of cancer genomes has revealed the extensive genetic heterogeneity and profound genomic instability of advanced neoplasms,<sup>1</sup> simultaneously suggesting that approaches that target late-stage lesions may be unrealistic and that treatments targeted to an earlier stage of disease – before such complexity manifests – may be more successful. After more than 50 years of cancer research, overall cancer mortality is declining at a rate of just 1.8% per year for men and 1.4% per year for women.<sup>5</sup> A common misperception plaguing the field of molecular cancer prevention is the notion that it is inappropriate to treat “healthy” individuals, where “healthy” is defined as the absence of clinical signs and symptoms of disease.<sup>3, 6</sup> However, asymptomatic individuals are not necessarily healthy and a more refined understanding among both the general public and health care providers regarding what constitutes “health” and “risk” as they relate to carcinogenesis and cancer will facilitate an emphasis on prevention and control of carcinogenesis, rather than treatment of invasive disease in isolation.<sup>6</sup>

The development of molecular preventive agents does not differ significantly from the development of therapies for advanced cancers, yet has unique challenges and special considerations.<sup>7</sup> The therapeutic index drives drug applications and is a function of the disease of interest, an agent’s intended and unintended effects, and patient susceptibilities to the disease and the agent’s effects. Achieving a positive risk/benefit ratio is particularly critical in prevention because it often (and most effectively) involves healthy or asymptomatic individuals; and because of the difficulty in predicting intermediate to long-term outcomes for individuals given both the time-constraints of the typical RCT and the inherent complexity of extrapolating the findings of group- and population- level data to individuals. Clinical trials of potential preventive agents, like therapeutic clinical trials, are designed to build a scientific premise, establish efficacy, explore/confirm safety, and achieve regulatory approval. However, important distinctions exist for each of the five primary determinants of clinical trial conduct – agents, biomarkers, cohorts, design, and endpoints (“ABCDEs”). While a detailed discussion of these elements in the context of molecular

preventive trials is beyond the scope of this review, several key considerations are highlighted here.

**Agents**—Perhaps one of the most important considerations in preventive trial design is the premise upon which the agent is being tested. Due to the involvement of asymptomatic individuals, in whom a lower threshold for risk can be expected, any agent to be tested in a preventive clinical trial, should integrate strong preclinical, mechanistic, and observational data whenever they're available.<sup>8</sup> As dosing frequencies, routes, attendant risks, and acceptable toxicities are narrower in the preventive setting than they are in the therapeutic setting, early clinical studies should clearly estimate the optimal dose, duration of treatment and potential toxicities before larger, more expensive trials are undertaken. Several key criteria have been established for potential preventive agents to fulfill (See Kelloff, et al.<sup>9</sup>); and there is often a need to adapt agents to be safer and more acceptable through a variety of strategies.

**Biomarkers**—Biomarkers allow us to assess the natural history of disease and the effects of an agent across several biologic levels (i.e., molecular, cellular, tissue), providing insights into efficacy and toxicity that can bolster clinical endpoints. However, the current shortage of validated, practical prevention-oriented intermediate biomarkers constitutes a significant barrier to continued progress in the field as well as to FDA approval of molecular preventive agents. The identification of biomarkers effective for both cancer risk and intermediate preventive response could considerably enhance the future development and approval of novel molecular preventive agents.

**Cohorts**—The selection of the study population often significantly impacts the outcome of prevention-based trials. Historically, trials were designed using average-risk populations, which necessitated large numbers of individuals and extended follow-up times. Such trials were costly and often resulted in null or even deleterious findings. Conversely, smaller trials focusing on high-risk populations provide increased power over shorter time frames, thereby increasing feasibility and reducing costs. Moreover, individuals at increased risk are typically both more tolerant of potential side-effects and more motivated to adhere to interventions and evaluations. Such trials are exemplified by some of the first chemopreventive trials investigating the use of NSAIDs to prevent familial forms of colorectal cancer.<sup>10–12</sup> Therefore, development of agents for individuals at increased risk has become a focus of the field.

**Design**—Trials that are appropriately designed isolate the agent as the primary study variable while holding all other variables constant. Randomized, controlled trials with compelling agents, cohorts and near-term endpoints are critical to advancing the field of molecular prevention. The use of a placebo arm allows for the natural history of the disease and of any biomarkers to be observed and assists in assessing the toxicity of an agent, which is crucial to the acceptability of the drug as a preventive agent. In addition, determining the degree to which trial participants adhered to the study protocol is important, as drop-ins and dropouts can affect a trial's power to assess its primary and secondary outcomes. Long-term monitoring and follow-up of both efficacy and safety with sufficient rigor to meet FDA

requirements is necessary to achieve regulatory approval and to promote acceptance in the marketplace. Sponsorship of a trial can also affect the overall design, as private investment, while often yielding more resources, can also lead to non-trivial concerns over potential bias. Finally, another important consideration in preventive trial design is the accessibility of the target organ, with trials of relatively inaccessible organs typically requiring larger sample sizes, longer durations and increased dependence on clinical, or image-based, rather than biological, efficacy markers. Indeed, only two of the FDA-approved preventive agents are for use in relatively inaccessible organs (e.g., tamoxifen and raloxifene in breast cancer), while six agents have been approved for use in skin, the most accessible organ (Table 1).

**Endpoints**—The selection of appropriate endpoints in preventive trials is both challenging and controversial. The development of cancer is a process often occurring over decades and in the context in which the identification of precursor lesions mandates interventions, such as surgical excision or ablation, altering the natural disease history and reducing cancer incidence. Consequently, the use of incidence and mortality endpoints is not always feasible, given the fiscal and temporal limitations of clinical trials and current standards of care. Therefore, many early phase preventive trials rely upon reductions in one or more measures of intraepithelial neoplastic lesions, such as changes in number, size, histopathology, or grading, as their primary endpoints. There remains a need for more immediate and practical endpoints in preventive trials. The identification of such endpoints could significantly drive public, but more importantly, private investment in the field.

## Current State of the Field

### Cancers with Agents Approved for the Treatment of Precancerous Lesions or Cancer Risk Reduction

**Breast**—Breast cancer is a heterogeneous disease that encompasses subtypes characterized by specific molecular biomarkers: estrogen receptor (ER)-positive; human epidermal growth factor receptor 2 (HER2)-positive; and triple-negative (“TNBC”; which are ER, progesterone receptor (PR), and HER2-negative) breast cancers. Due to the disparity in efficacy of prevention agents for each of these distinct tumor types, we will discuss the major chemoprevention approaches currently in clinical use, or with high potential in the near future, by each specific subtype individually. Phase III trials are shown in Table 3.

#### ER-positive Breast Cancer

**Selective Estrogen Receptor Modulators (SERMs):** SERMs represent the first successful agents for the prevention of breast cancer. As these are estrogen receptor modulators, by definition these are most effective for patients at high risk of ER-positive breast cancer. Following positive results from clinical treatment trials investigating tamoxifen in women with early stage breast cancer, several phase III breast cancer prevention trials were conducted studying the effectiveness of tamoxifen for women at high-risk of breast cancer. The results of these studies demonstrated that tamoxifen reduces invasive ER-positive breast cancer by 30–60%,<sup>18–21</sup> and led to FDA approval for the use of tamoxifen in high-risk women for breast cancer risk reduction (Table 1). While tamoxifen prevents the development of many ER-positive breast cancers, many women choose not to take tamoxifen because of

concerns about its side effects, including hot flushes, vaginal dryness and discharge, increased risk of cataracts, and rare side effects, such as increased incidence of blood clots (deep venous thrombosis, pulmonary emboli, transient ischemic attack (TIAs), or stroke) and increased risk of uterine cancer. Data from trials of tamoxifen in the adjuvant setting suggest a dose- and duration-dependent risk of side-effects. Consequently, work is on-going in the preventive setting to optimize the tamoxifen regimen through dose reduction, combinations with other agents, intermittent dosing, and/or topical administration.<sup>22</sup>

Treatment with the second generation SERM raloxifene was found to produce similar preventive effects as tamoxifen (a 45–90% decrease in invasive ER-positive tumors) and with reduced side effects, including no increase in the risk of uterine cancer.<sup>23–25</sup> These studies resulted in the FDA approval of raloxifene as an alternative treatment to tamoxifen for breast cancer risk reduction in high-risk women (Table 1). However, treatment with raloxifene is still associated with increased risk of hot flushes and thromboembolic/ cardiovascular events. In addition, its preventive effects degrade after three years to retain only 76% of the effectiveness of tamoxifen for the prevention of all breast cancers, and 78% of the effectiveness of tamoxifen for the prevention of noninvasive DCIS breast cancers.<sup>26, 27</sup> Given that there appears to be a trade-off between side-effects and effectiveness over the long-term, the selection of tamoxifen versus raloxifene as a preventive therapy is dependent upon the patient. As it is less likely to cause uterine cancer than is tamoxifen, raloxifene may be best for post-menopausal women at high-risk of breast cancer with an intact uterus. However, in post-menopausal women without a uterus, tamoxifen may be the drug of choice since it shows enhanced effectiveness over the long-term.

Following these landmark clinical trials, third generation SERMs were investigated for their cancer preventive effects. The Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene (PEARL) Trial studied the effects of lasofoxifene, a SERM developed for the treatment of osteoporosis, as a breast cancer preventive agent in postmenopausal women with low bone mineral density (BMD).<sup>28, 29</sup> The results of this phase III clinical prevention trial showed a 79% reduction in invasive breast cancer and an 83% reduction in ER-positive breast cancer in patients treated with lasofoxifene. A similar phase III prevention trial, known as the Generations Trial, reported a 56% decrease in invasive breast cancers in postmenopausal women with low BMD treated with arzoxifene, a SERM developed to maintain bone density in patients with osteoporosis.<sup>30, 31</sup> These trials found that both lasofoxifene and arzoxifene reduce risk of nonvertebral and vertebral fractures; however, these third generation SERMs, like raloxifene and tamoxifen, still increase risk of venous thromboembolic events.<sup>28–31</sup> To date, neither lasofoxifene or arzoxifene has been approved for clinical use by the FDA.

A meta-analysis conducted by Cuzick and colleagues was recently published that included all nine of the large-scale phase III SERM prevention trials.<sup>32</sup> This comparative analysis demonstrates that overall breast cancer incidence is decreased by SERMs, although this was due to a reduction in ER-positive breast cancers, and that DCIS incidence is decreased by all analyzed SERMs, except raloxifene. Cuzick and colleagues also analyzed adverse events associated with these SERMs and found that SERMs are associated with decreased vertebral fractures (494 v. 798 events across 9 SERM trials; OR=0.66, 95% CI: 0.59–0.73), but

increased endometrial cancer (105 v. 63 events across 9 SERM trials; HR=1.56, 95% CI: 1.13–2.14) and venous thromboembolic events (375 v. 215 events across 9 SERM trials; OR=1.73, 95% CI: 1.47–2.05).<sup>32</sup> Extended follow-up of the IBIS-I trial, with a median follow-up time of 16 years, did not identify any new late toxicities and demonstrated a substantially improved benefit-harm balance for tamoxifen over the long-term.<sup>33</sup> Unfortunately, none of the SERM-based preventive interventions decrease risk of ER-negative breast cancer.

**Aromatase Inhibitors (AIs):** While SERMs modulate estrogenic activity, AIs block the aromatase enzyme, inhibiting the conversion of androgen into estrogen. Clinical trials investigating the effectiveness of AIs for treating women with hormone receptor-positive breast cancer (e.g., the ATAC trial<sup>34, 35</sup>) have demonstrated improved results with AIs as compared to SERMs. These positive results led to phase III trials testing the preventive efficacy of AIs (e.g., exemestane and anastrozole) for breast cancer development in high-risk women. the development of breast cancer in high-risk women.<sup>35–38</sup> The first of the AI prevention trials to be reported was the NCIC-MAP3 trial in which postmenopausal women at high risk of breast cancer were treated daily with exemestane or placebo for 5 years.<sup>38</sup> The results showed that exemestane reduced incidence of invasive breast cancer by 65% and of ER-positive breast cancer by 73%. As with the SERM-based trials, there was no reduction in incidence of ER-negative breast cancer. A second prevention trial testing the AI anastrozole in high-risk postmenopausal women demonstrated a 53% reduction in incidence of all breast cancer, a 50% reduction in the incidence of invasive breast cancer, and a 58% reduction in ER-positive breast cancer.<sup>37</sup> As with the exemestane trial, no significant reduction in the incidence of ER-negative breast cancer was seen. To date, none of the AIs have been approved by the FDA for breast cancer risk reduction.

AIs are also being tested in women with previous DCIS to determine whether they will reduce breast cancer recurrence or the development of new contralateral breast tumors. Two studies comparing anastrozole with tamoxifen in postmenopausal women with previous DCIS, the NSABP B-35 trial (NCT00053898) and the IBIS-II (DCIS) trial,<sup>35</sup> are currently ongoing. While both of these studies have reached their accrual goals, further follow-up is needed before analyzing the results.

**HER2-positive Breast Cancer:** Several trials have tested whether drugs targeting the HER2 oncogene will be useful for breast cancer prevention. The first trial, reported by Kuerer and coworkers in 2011, was a pilot study of the anti-HER2 drug, trastuzumab, in patients with HER2-positive DCIS.<sup>39</sup> In this trial, women were given a single dose of trastuzumab or placebo 14–28 days prior to excisional surgery. No change in the size or growth rate of the excised HER2-positive DCIS was seen; however, immunologic responses were observed. This study was followed by a phase III trial of trastuzumab comparing 2 doses of trastuzumab in combination with radiation therapy versus radiation therapy alone in women with HER2-positive DCIS breast cancer, the results of which are expected within the next few years.

Several other phase II trials have tested the anti-HER2 drug lapatinib, which inhibits both the EGFR and HER2 tyrosine receptor kinases. Preclinical studies have shown that lapatinib

can prevent the development of HER2-positive breast tumors in mice.<sup>40</sup> DeCensi and coworkers conducted a pre-surgical phase II trial in women with invasive or non-invasive HER2-positive breast cancer testing the ability of lapatinib or placebo to suppress breast cancer cell growth.<sup>41</sup> They showed that lapatinib was able to inhibit proliferation in both invasive and non-invasive breast cancers. A second pre-surgical phase II trial in women with HER2-positive or EGFR-positive DCIS breast cancer is ongoing (NCT0055152). These studies will provide the rationale to test anti-HER2 therapies in women with HER2-positive DCIS breast cancer in future phase III prevention trials.

**Prevention of TNBC:** While anti-estrogen drugs have been shown to prevent ER-positive breast cancers, and HER2- targeted drugs show promise in early trials for the prevention of HER2-positive breast cancers, there are no preventive interventions for ER-negative, PR-negative, and HER2-negative, or “triple-negative”, breast cancers. Preclinical and early clinical trials suggest a number of agents that may have the potential to prevent these cancers, including the Cox-2 inhibitor celecoxib, retinoids, statins, epigallocatechin gallate (EGCG; the active agent in green tea), and the anti-diabetic drug metformin.<sup>42–52</sup> Further clinical development of celecoxib and retinoids has been hindered by their associated toxicities.<sup>53–57</sup> Metformin (850mg twice a day vs. placebo) is currently being tested in a phase III trial (NCT01101438) as adjuvant therapy in women with resected early stage breast cancer. Patients will be stratified according to hormone receptor and HER2 receptor status and results may provide important information for the future development of metformin for the tertiary prevention of breast cancer, including TNBC. Phase III trials testing statins or ECGC in the prevention of any molecular sub-type of breast cancer have yet to be conducted. Despite the identification of effective chemopreventive agents for ER-positive breast cancers, no agent to date has been shown to prevent TNBC in humans.

As summarized in Table 3, SERMs and AIs have demonstrated significant efficacy in phase III chemoprevention trials specifically designed to assess their cancer preventive effects. However, they only prevent ER-positive breast cancers. The SERMs tamoxifen and raloxifene remain the two risk-reducing medications available for clinical use (Table 1), but uptake in at-risk populations remains low due to concerns over toxicity and a perceived unfavorable balance between risks and benefits. None of the AIs have been approved by the FDA to date. However, exemestane and anastrozole are being used rarely for breast cancer prevention (in off label use). The United States Preventive Services Task Force (USPSTF) currently recommends that clinicians engage in shared, informed decision making and offer to prescribe these medicines for women aged 35 and older who are at an increased risk of the disease and at low risk of adverse medication effects.<sup>58</sup> This is a grade B recommendation, indicating that there is high certainty that the net benefit is moderate or that there is moderate certainty that the net benefit is moderate to substantial from the use of tamoxifen and raloxifene to reduce the incidence of invasive breast cancer in women who are at increased risk for this disease.<sup>58</sup> Recent data from a 2013 meta-analysis of all nine SERM trials<sup>32</sup> and from extended follow-up of the IBIS-1 trial<sup>33</sup> suggest a much more favorable benefit-harm balance over the long term than in the short term, with an estimated 22 women requiring treatment for five years to prevent one breast cancer in the next 20 years.<sup>33</sup> Whether such data will help to improve rates of uptake in at-risk populations



remains to be seen, but such findings emphasize the importance of considering all benefits and all risks over the lifespan when evaluating whether or not to provide a preventive intervention.

**Cervix**—Since the introduction of the Papanicolaou (Pap) test for cervical cancer screening, both incidence and death rates for cervical cancer have been declining.<sup>59</sup> Yet, cervical cancer remains a major cause of cancer-related death throughout the world, particularly in low and middle-income countries.<sup>60</sup> While cervical cancer screening remains critical for cervical cancer prevention in the U.S. and around the world, the HPV vaccines offers an important molecular prevention option for cervical cancer as well as other ano-genital cancers. The HPV vaccines represent the first vaccines to be marketed as “cancer prevention” vaccines.

**Vaccine Trials:** The sexually transmitted human papillomavirus (HPV) represents the leading sexually transmitted disease in the U.S. and is now known to be the predominant cause of cervical cancer.<sup>61–64</sup> Seventy per cent of cervical cancer diagnoses result from HPV16 and HPV18, two of the nine high-risk HPV subtypes, all of which are now deemed carcinogenic.<sup>61</sup> HPV 16 and 18 have also been shown to cause vaginal, vulvar, penile, oropharyngeal, and most anal cancers, while HPV6 and 11 cause 90% of genital warts.<sup>65</sup>

The prophylactic HPV vaccine administered prior to HPV infection has been shown to significantly reduce both cervical cancer and cervical intraepithelial neoplasia (CIN), as well as cancers of the vulva and vagina, particularly if administered to individuals prior to their first sexual activity.<sup>66, 67</sup> Koutsky and colleagues analyzed the preventive effects of an HPV16-specific vaccine versus placebo in 2,392 women 16–23 years of age on incidence of HPV16 infection.<sup>68</sup> This study showed HPV16 incidence rates of 0 and 3.8 per 100 women in the HPV16 vaccine and placebo groups, respectively (100% efficacy; 95%CI, 90–100).

Following the success of the univalent HPV16 vaccine, Koutsky and colleagues conducted the phase III Females United to Unilaterally Reduce Endo/Ectocervical Disease (Future II) clinical trial. This study tested effectiveness of the quadrivalent HPV6/11/16/18 vaccine Gardasil® versus placebo in more than 12,000 women between the ages of 16 and 26 for the prevention of high-grade HPV16/18-related cervical lesions.<sup>69</sup> The study was terminated early due to the significant reduction of HPV-related high-grade CIN within the treatment arm (100% efficacy for both CIN grade 2 and adenocarcinoma *in situ*, and 97% efficacy for CIN grade 3, versus placebo). Furthermore, vaccination of women infected with one or more of the four HPV types targeted by Gardasil prior to vaccination, developed resistance to the remaining HPV types with which they were not infected. The vaccine also demonstrated 99% preventive efficacy for genital warts. Side effects were limited, and adverse events were predominantly injection-site pain (vaccine group 84%, placebo group 77.9%; 95%CI, 1.4–11.7).

Other clinical trials have shown similar positive results for HPV vaccine-based studies.<sup>70–74</sup> Bivalent vaccine safety has since been evaluated across 11 clinical trials,<sup>75</sup> as well as in a meta-analysis of bivalent and other vaccines,<sup>76</sup> which reported the most common adverse events of vaccine versus control groups to include injection-site symptoms, fatigue,

headache and myalgia, with no statistical difference between treatment groups for all serious adverse events and deaths reported.

Based on the efficacy and tolerability reported in large clinical trials of non-HPV infected subjects, the FDA approved Gardasil® (MERCK) for the prevention of HPV6, 11, 16, and 18 in 2006, and Cervarix® (GlaxoSmithKline; GSK) for the prevention of HPV16 and 18 in 2009 (Table 1). Recommendations for HPV vaccine use were subsequently released by the US Preventive Services Task Force,<sup>77</sup> the American Society for Clinical Pathology and the American Society for Colposcopy and Cervical Pathology.<sup>78</sup> The American Cancer Society currently recommends that women be vaccinated for HPV at 11–12 years of age and, with a physician's recommendation, as early as 9 or between the ages of 19 and 26.

Gardasil® has also been shown to prevent HPV-related precancerous lesions, genital warts and anal and penile cancers in men, and may prevent head and neck cancer.<sup>79</sup> This preventive efficacy for cancers among the male population has resulted in the recommendation of the Advisory Committee on Immunization Practices (ACIP) for the three-dose HPV vaccination series for males 11–12 years of age, which may be initiated as early as 9 years of age or for males 13–26 years of age upon physician consultation.<sup>66</sup> However, the cost-effectiveness of vaccinating males is not as well-established as that for vaccinating females at the current recommended ages.<sup>80</sup> The consensus to date is that the cost-effectiveness of male vaccination is greater when vaccine coverage is low in females and when all potential health benefits are included in the analysis.<sup>80</sup>

In December 2014, the FDA approved the upgraded Gardasil®9 vaccine, which expands protection of the quadrivalent vaccine to five additional HPV strains (31, 33, 45, 52, and 58) and can potentially prevent approximately 90% of cervical, vulvar, vaginal, and anal cancers.<sup>81</sup> In an RCT of more than 12,000 boys and girls, Gardasil®9 demonstrated 97% efficacy in preventing cervical, vulvar and vaginal cancers caused by the five additional strains; and was equally effective as the quadrivalent vaccine in preventing the cancers and genital warts caused by the four HPV types shared between the vaccines.<sup>82</sup>

**Chemoprevention-based Studies:** Prior to the development of the HPV vaccine, the focus of chemopreventive efforts around cervical cancer focused on retinoids, various micronutrients, the polyamine synthesis inhibitor difluoromethylornithine (DFMO), and the adduct reducer Indole-3-carbinol. However, results of these studies were disappointing. It is likely that the HPV vaccine, with continued pap screening, will become the foundation of cervical cancer prevention.

**Esophageal**—The two predominant histological subtypes of esophageal cancer are esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). ESCC is the most prevalent subtype in developing countries, but EAC is predominant in the U.S. and other westernized nations. Secondary prevention of esophageal cancer is based upon endoscopic screening and early detection in high-risk individuals, with subsequent treatment of precancerous lesions or early stage disease using excisional or ablative techniques. In 2003, the FDA approved Photofrin to be used with photodynamic therapy (PDT) for the treatment of high-grade dysplasia in BE patients (Table 1). However, PDT is

being replaced by radiofrequency ablation (RFA) with mucosal resection as the current endoscopic standard of care due to RFA's improved efficacy and safety results.<sup>83, 84</sup> Primary prevention through risk factor reduction and chemoprevention based upon micronutrients, in the case of ESCC, and aspirin or other NSAIDs, in the case of EAC, is the goal.

**Esophageal Squamous Cell Carcinoma (ESCC):** Many nutrition supplement trials testing different combinations of vitamins and minerals have been conducted among residents of Linxian, China, a population at very high risk of ESCC.<sup>85-91</sup> The largest of these, conducted by Blot et al., examined five years (1986–1991) of treatment with four different vitamin and mineral combinations, at doses of 1–2 times the U.S. recommended daily allowances, in approximately 30,000 individuals.<sup>92</sup> None of the vitamin-mineral combinations significantly decreased ESCC incidence or mortality, although riboflavin plus niacin resulted in a borderline-significant 14% reduction in incidence ( $p=0.06$ ). A combination of selenium, beta-carotene and vitamin E supplements (which significantly decreases both gastric and total cancer deaths) resulted in a non-significant 4% reduction in ESCC deaths.<sup>92</sup> After a fifteen-year follow-up, this same combination showed a significant 17% reduction in ESCC mortality in individuals <55 years of age, but increased mortality in individuals ≥55.<sup>93</sup> Limburg more recently tested the ability of 10 months of treatment with selenomethionine (200mcg q.d.) and celecoxib (200 mg b.i.d.) to improve mild or moderate squamous dysplasia (accepted histological precursor to ESCC) in a 2×2 factorial RCT of 267 Linxian residents.<sup>94</sup> While celecoxib failed to exhibit any effect on either mild or moderate dysplasia, selenomethionine resulted in a significant improvement ( $p= 0.02$ ) in mild dysplasia.<sup>94</sup>

These trials suggest that vitamin or mineral supplements in nutritionally-compromised populations at high risk for ESCC may have preventive potential. Nevertheless, due to a host of complexities related to the agents, population and endpoints used, a recommended clinical regimen for the prevention of ESCC has yet to be established. A number of other agents have demonstrated preventive potential in *in vivo* ESCC models, including ellagic acid, diallyl sulfide, tea-related theaflavins, curcumin, resveratrol, irinotecan, isothiocyanates, and COX inhibitors.<sup>95</sup>

**Esophageal Adenocarcinoma (EAC):** Only one Phase IIb chemopreventive RCT has been conducted for EAC, despite its incidence increasing by 463% and 335% among white males and females, respectively, in the U.S. between the periods of 1975–1979 and 2000–2004.<sup>96</sup> A lack of convincing EAC animal models has hindered the identification and development of chemopreventive agents for this disease. Heath et al. compared celecoxib (200mg b.i.d. for 48 weeks) to placebo in 100 patients with Barrett's esophagus (BE; a neoplastic precursor to EAC).<sup>97</sup> Study results demonstrated no difference in dysplasia regression between study arms; however, quantitative endoscopic data suggest a reduction in the BE surface area in the celecoxib group after one year of treatment.<sup>97, 98</sup> The largest Phase III EAC trial is the Aspirin Esomeprazole Chemoprevention Trial (AspECT), a large, multi-center trial testing the chemopreventive effect of the proton-pump inhibitor esomeprazole (20 or 80 mg b.i.d.) with or without aspirin (300mg q.d.) in reducing either all-cause

mortality or the conversion rate from Barrett's metaplasia to adenocarcinoma or high grade dysplasia.<sup>99</sup> The trial began in 2006, and interim results are expected soon.

**Colon**—Although other agents have demonstrated some degree of protection within the colorectum in RCTs (Table 3), non-steroidal anti-inflammatory drugs (NSAIDs) have been and continue to be the focus of chemopreventive agent development for colorectal cancer (CRC), given the well-established role of inflammation and the COX enzymes in colorectal neoplasia, as well as the plethora of preclinical and observational data suggesting the preventive efficacy of aspirin and NSAIDs against colorectal cancer and possibly other cancers.<sup>100</sup> Trials typically assess recurrent adenomas as the endpoint, or more rarely, CRC incidence or mortality. The use of adenomas as a reasonable intermediate, if not definitive, preventive endpoint is supported by multiple lines of evidence.<sup>101–104</sup>

Large, population-based trials of alternate-day aspirin use from the Women's Health Study (WHS; 100 mg) and the Physician's Health Study (PHS; 325 mg) did not initially demonstrate significant effects of aspirin in the primary prevention of CRC, after 10 and 5 years of treatment, respectively.<sup>105, 106</sup> Results from the PHS remained null after 12 years of follow-up.<sup>107</sup> However, after an overall follow-up time of 18 years, recent results from the WHS indicate a significantly reduced risk for colorectal cancer in healthy women (HR=0.80; 95% CI=0.67–0.97,  $P=0.021$ ).<sup>108</sup> Pooled analyses of trials of daily aspirin use in the context of cardiovascular disease have demonstrated significant reductions in CRC incidence and mortality, primarily in those using aspirin for five or more years and after a latency of 10 years.<sup>109, 110</sup> Three smaller trials in individuals with a prior history of adenomas demonstrated a 20%–30% reduction in risk of recurrent adenomas after one to three years of follow-up.<sup>111–113</sup> Risk reduction in each trial was generally greater for advanced and/or large (>5mm) adenomas.<sup>111–113</sup> However, follow-up results of one of the trials<sup>112</sup> did not confirm these initial findings, citing no significant differences between the aspirin and placebo groups after four years of treatment.<sup>114</sup> Another trial of individuals with prior resected early-stage CRC identified a significant 35% reduction in adenoma incidence after three years of treatment with aspirin (325mg q.d.) given in an adjuvant context.<sup>115</sup> The CAPP-1 and CAPP-2 trials examined aspirin (600mg q.d.) in subjects with the hereditary CRC syndromes of Familial Adenomatous Polyposis (FAP) and Lynch Syndrome, respectively.<sup>116, 117</sup> CAPP-1 identified a non-significant reduction (23%) in polyp count and a trend towards reduced largest polyp size within the aspirin-treated group, after a median of 17 months of intervention.<sup>116</sup> CAPP-2 found a significant reduction in risk of CRC (59%) only in subjects completing at least two years of intervention after a mean of 55.7 months of follow-up.<sup>117</sup> The CAPP-3 trial will compare the effect of different doses of aspirin in Lynch Syndrome.<sup>117</sup>

Although the dose and duration of aspirin differ among the trials, overall, data from RCTs supports the use of aspirin to protect against CRC and is in agreement with much of the observational data. While observational data may suggest that longer time frames are required to see a preventive effect, effects on adenomas can be seen in one to three years when endoscopies are performed on schedule, as part of an RCT protocol.<sup>118</sup> Additional trials are needed to determine the optimum dosing regimen and answer remaining questions regarding which molecular subtypes of colorectal cancer might be prevented. Observational

data have already suggested that the benefit of aspirin may be dependent upon mutations in *PIK3CA* in individuals with a diagnosis of colon cancer; and familial data suggests that a mutation in *SLCO2A1*, a member of the prostaglandin catabolic pathway, is associated with early colonic neoplasia and NSAID resistance.<sup>119, 120</sup>

In addition to aspirin, COX-2 inhibitors and sulindac have also demonstrated efficacy in RCTs. Celecoxib has been tested in three trials: a small trial of 77 FAP patients,<sup>10</sup> and the subsequent Adenoma Prevention with Celecoxib (APC)<sup>118</sup> and Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP)<sup>121</sup> trials of individuals with a history of adenomas. The FAP study demonstrated significant decreases in polyp number and overall polyp burden following six months of treatment with celecoxib (400mg b.i.d.),<sup>10</sup> and led to the interim approval of celecoxib as an adjunct to endoscopic and surgical treatment of FAP patients (Table 1). However, the labeled indication for polyp management in FAP patients was sacrificed due to challenges in conducting confirmatory trials in this high-risk setting. Subsequently, significant protective effects were also observed in the APC and PreSAP trials.<sup>118, 121</sup> However, both trials identified up to a 2–3-fold higher risk of serious cardiovascular events among those taking celecoxib.<sup>118, 121</sup> Later post-hoc analyses of six publically funded trials suggested that this risk may be restricted to those with an elevated baseline risk of cardiovascular disease.<sup>122, 123</sup> Nevertheless, as CRC and cardiovascular disease share a number of risk factors and definitive data are lacking, celecoxib is not currently recommended for the prevention of CRC.

Sulindac has demonstrated mixed results in four small trials involving FAP patients, ranging in size from 10–44 individuals. A primary prevention trial testing the ability of four years of sulindac treatment to prevent adenoma development or reduce the number and/or size of adenomas in phenotypically-unaffected FAP carriers of the FAP genotype failed to demonstrate an effect.<sup>124</sup> However, results from secondary prevention trials have been largely positive, with three trials demonstrating a protective effect of sulindac on the number, size and regression of adenomas.<sup>12, 125, 126</sup> A fourth trial in individuals with sporadic adenomas did not show a significant effect on adenoma regression after four months of treatment.<sup>127</sup>

The harms associated with the long-term use of NSAIDs are well-established and include gastrointestinal and cardiovascular toxicities. A recent meta-analysis of 280 trials of NSAIDs versus placebo and 474 trials of one NSAID versus another NSAID demonstrated that all NSAID regimens increased upper gastrointestinal complications; and that coxibs and diclofenac significantly increased vascular events, primarily major coronary events, as well as vascular death.<sup>128</sup> However, the meta-analysis also showed that these risks can be predicted once the baseline risks for such hazards are known, which could allow for tailoring of the use of these medicines, and as the authors state, aid in clinical decision making.<sup>128</sup> Although rare, another potential side-effect of prolonged NSAID use is Diaphragm Disease, characterized by short, circumferential lesions most commonly located in the small intestine and which cause luminal stenoses.<sup>129, 130</sup> In a study using capsule enteroscopy, 2% of those on traditional NSAIDs showed evidence of strictures in the small bowel, while those on COX-2 inhibitors did not exhibit such strictures.<sup>131</sup> Overall, 1% of all patients taking NSAIDs had strictures.<sup>131</sup> Notably, such strictures have also been seen in those in which

NSAID use could not be proven.<sup>129</sup> It has been suggested that the formation of diaphragms may be a non-specific response to various insults to the intestine.<sup>129</sup> In 2007, the USPSTF recommended against the use of aspirin and NSAIDs to prevent CRC in those at average risk of the disease, as they concluded that overall there was good evidence of at least moderate harms associated with their use.<sup>132</sup> The Task Force is currently in the process of updating this recommendation with regard to aspirin.

In addition to NSAIDs, calcium has also exhibited a significant protective effect against adenomas. In a placebo-controlled RCT by Baron et al., calcium carbonate (3g daily [1200 mg elemental calcium]) given over four years to individuals with recently resected adenomas demonstrated a 19% reduction in re-current adenomas.<sup>133</sup> However, in a recent and larger RCT of both calcium and vitamin D over three to five years, Baron, et al. found these agents to be ineffective in reducing the risk of colorectal adenomas. (Abstract CT335, presented at 2014 AACR Annual Meeting)

Colorectal chemoprevention has also provided a forward-looking opportunity to test agent combinations, which are widely anticipated to be more effective in prevention, based upon exciting preclinical data<sup>134–136</sup>, and the dominant role of therapeutic combinations in cancer treatment. Sulindac was tested in combination with DFMO in 375 individuals with sporadic adenomas.<sup>137</sup> Combined sulindac-DFMO treatment proved successful, resulting in a remarkable 70% reduction in recurrent adenomas versus placebo, with no significant differences in adverse effects.<sup>137</sup> As this first study illustrates, agent combinations hold tremendous promise for the future of chemoprevention by increasing efficacy, decreasing toxicity or both. RCTs of various agent combinations are underway, including: sulindac and DFMO in the setting of FAP (NCT01483144) and in those with previous resected CRC (NCT01349881), a trial of DFMO in conjunction with aspirin (NCT00983580) in those with current or previous adenomas, and trials of DFMO and celecoxib (NCT00033371) and sulindac and erlotinib (NCT01187901) in FAP patients.

In addition to those with FAP and Lynch Syndrome, individuals with inflammatory bowel disease (IBD), either Ulcerative Colitis (UC) or Crohn's Disease (CD), also have an increased risk of colon cancer compared to the general population, although estimates vary as to the magnitude of this risk.<sup>138</sup> As a means of secondary CRC prevention in this population, endoscopic surveillance is recommended for patients with long-standing disease. However, the extent of colonic inflammation often present in these patients can make it difficult to detect precancerous and cancerous lesions. Various agents have been tested for the primary prevention of CRC in the setting of IBD, although none in phase III trials. And observational data on many of these agents are inconclusive. 5-Aminosalicylate (5-ASA) is the first-line therapy for the treatment of mild to moderate UC and has perhaps been studied most extensively with regard to its preventive properties in IBD. Some reports have suggested it reduces the incidence of CRC in this context, although other studies have suggested no effect.<sup>138</sup> Three meta-analyses have been conducted on the topic, with two of them finding significant protective effects of 5-ASA on CRC or colorectal neoplasia in UC,<sup>139, 140</sup> and one finding a significant protective effect in clinic-based populations but not in non-referral populations.<sup>141</sup> Conducting a RCT of 5-ASA is challenged by the fact that it serves as first-line therapy for UC, precluding a proper control group. Nevertheless, its

favorable safety profile and strong biologic plausibility support its continued investigation as a possible preventive agent for CRC in the setting of UC.<sup>138</sup> Aside from 5-ASA, ursodeoxycholic acid (UDCA) also shows some promise in this area. A few early observational studies and two recent meta-analyses suggest UDCA may prevent CRC in IBD, particularly in those patients who also have primary sclerosing cholangitis (PSC).<sup>138,142, 143</sup> However, some data suggest that high-doses of UDCA may actually increase the risk of CRC in UC patients with PSC.<sup>144</sup> But again, its strong biologic plausibility supports its continued investigation for use in IBD to reduce the risk of CRC. Further studies are warranted for both 5-ASA and UDCA.

**Bladder**—As much as 80% of urothelial tumors at presentation are non-muscle invasive bladder cancer (NMIBC), otherwise considered “precancerous” in most other organs.<sup>145</sup> Valrubicin and Bacillus-Calmette-Guerin (BCG) were developed as adjuvant therapies for the treatment of preinvasive neoplastic lesions, rather than for a specific preventive indication. BCG is the standard of care after transurethral resection (TUR) of high-risk NMIBC. It was initially developed as a vaccination against tuberculosis. In 1976, Morales, et al. reported its use in a pilot study of six weekly instillations of intravesical BCG use in nine patients with recurrent bladder cancer.<sup>146</sup> Following this, small RCTs by Lamm et al. and Pinsky et al. found that BCG reduced tumor recurrence.<sup>147, 148</sup> An RCT by Herr, et al. of 86 patients with superficial bladder cancer found intravesical BCG with TUR could significantly delay disease progression and increase overall survival in comparison to TUR alone.<sup>149</sup> Ten-year follow-up data from this RCT confirmed these findings, with a 10-year disease-specific survival rate of 75%, compared to a rate of 55% in those receiving TUR alone.<sup>150</sup> A number of RCTs have examined the clinical benefit and optimal regimen of maintenance therapy in comparison to induction therapy alone.<sup>151</sup> However, because of the small size of many of these studies, results are difficult to interpret. The largest study by Lamm, et al. of 384 patients demonstrated that patients receiving the 3-week, 3-year maintenance regimen had median recurrence-free survival times twice as long as those who did not receive maintenance; and those in the maintenance group also had significantly longer worsening-free survival times (Table 3).<sup>152</sup> This study serves as the basis for the currently used 3-year maintenance protocol. Nevertheless, a 2013 critique of the evidence suggests that additional larger RCTs are needed to determine the optimal duration of maintenance therapy based on tumor risk factors.<sup>151</sup>

Valrubicin offers a second line of treatment for patients with BCG-refractory carcinoma in situ (CIS) of the bladder in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality. Steinberg, et al. reported results from a multi-institutional non-comparative study of 90 patients with CIS who failed at least 2 courses of intravesical therapy, at least one of which was BCG. Findings demonstrated that six weekly instillations of 800mg of valrubicin was well-tolerated and that 21% of patients remained disease-free six months after treatment, and responses were durable, with a median response time greater than 18 months.<sup>153</sup> These data were subsequently revised but only reported in the FDA prescribing information. Consequently, in 2013, Dinney et al. provided an updated report on the safety and efficacy of valrubicin based on the revised phase III trial data along with data from a supportive phase II/III trial (A9303 trial). Based on the updates to the data

originally reported in Steinberg, et al.,<sup>153</sup> the complete response rate changed from 21% to 18%, which is identical to the CR reported in the supportive A9303 trial by Dinney et al.<sup>154</sup> The supportive trial also demonstrated a disease-free status of 22% at six months, 10% at one year, and 4% at two years.<sup>154</sup> Because patients in the A9303 trial were less highly treated than in the previous phase III trial, Dinney et al. conclude that valrubicin is both safe and efficacious in highly pretreated populations as well as those with few previous therapies.<sup>154</sup> The identification of subsets of NMIBC patients based on molecular profiling may allow for more tailored treatment resulting in better outcomes for this condition.

**Skin**—Skin cancer is the most common site of malignancy in humans. By virtue of how commonplace and accessible these cancers are, skin has been a favored site for the development of chemoprevention agents, particularly for non-melanoma skin cancers (NMSC). Importantly, two specific skin cancers, cutaneous squamous cell carcinoma and melanoma, have strong clinico-pathologic evidence for developmental sequences that proceed through preneoplastic intermediates, thus enabling targeting the treatment of specific preneoplastic lesions for cancer prevention.

**Actinic Keratoses and Cutaneous Squamous Cell Carcinoma:** Cutaneous squamous cell carcinoma (cSCC) comprises 15–20% of skin cancer cases, numbering over 700,000 per year in the U.S.<sup>155, 156</sup> Importantly, cSCC has the most accessible and clinically well-characterized progression sequence of any human cancer, progressing from a distinct precancerous lesion, the actinic keratosis, to invasive carcinoma. Actinic keratoses (AKs) are the most common precancerous lesion in humans,<sup>157</sup> affecting upwards of 5.5% of women and 13.9% of men in the U.S., and accounting for 5.2 million visits per year and an estimated annual cost of \$920 million.<sup>158</sup> Approximately 65%–72% of cSCCs arise in association with preneoplastic AKs,<sup>159</sup> indicating that interrupting progression at this stage would be a clinically important intervention.

In accordance with this, there are several modalities frequently used for treating AKs. Many are purely destructive such as electrodesiccation, curettage, cryosurgery, or chemical peels.<sup>160</sup> Five active topical agents are currently FDA-approved for the treatment of AKs: 5-fluorouracil cream, diclofenac gel, imiquimod cream, ingenol mebutate gel, and delta-aminolevulinic acid photodynamic therapy (PDT) (Table 1; Masoprocol was withdrawn from the U.S. market in 1996). Despite many randomized placebo-controlled trials for these modalities, there have been no head-to-head comparisons of any of the field-directed topical therapies.<sup>161</sup> Overall, their individual efficacy in clearing AKs is comparable, with differences in adverse effects and cosmesis.<sup>161</sup> None of these agents has been studied in a phase III randomized trial to prove efficacy in the prevention of NMSC as a primary endpoint, as any expected benefit on AKs has been largely assumed to result in a reduction in cSCC/basal cell carcinoma (BCC) incidence and changes in AKs have been interpreted as a sufficient “clinical benefit”.<sup>161</sup>

Retinoids represent the most commonly tested agent in advanced RCTs for the prevention of AK and NMSC (Table 3). Overall, the preventive efficacy of systemic and topical retinoids against new NMSC or new and extant AKs has been modest, with the greatest benefit observed for acitretin in renal transplant patients (36% difference in cSCC incidence), a high



risk group.<sup>162</sup> This benefit was not observed in a recent trial of acitretin in nontransplant patients.<sup>163</sup> Similarly, a recent trial of topical tretinoin cream involving 1,191 veterans showed no benefit in lowering AK, BCC, or cSCC incidence, with a greater number of skin-related adverse events.<sup>164</sup> Moreover, a follow-up analysis of one trial concluded that a certain dose range of retinol was associated with higher incidences of cSCC, suggesting incompletely understood biological effects of manipulating retinoid signaling.<sup>165</sup> Another potential disadvantage of retinoids is that discontinuation is associated with a rebound effect and quick loss of the preventive effect.<sup>165</sup>

There is abundant preclinical evidence for cancer chemopreventive efficacy of COX-2 inhibition in skin and in the GI tract, and while a large phase III trial demonstrated no benefit in reducing AK incidence during and following 9 months of celecoxib (200mg q.d.), there were significant reductions in both BCC (RR=0.40, 95% CI=0.18–0.93,  $p=0.032$ ) and cSCC (RR=0.42, 95% CI=0.19–0.93,  $p=0.032$ ) incidence.<sup>166</sup> Although no difference in the numbers of cardiovascular events was observed in this trial, the required FDA boxed warning of serious or life-threatening adverse effects associated with celecoxib is unlikely to enable further investigation in this arena, and the precise antineoplastic mechanism(s) of the drug remain unclear.<sup>167</sup> Topical diclofenac is also a COX-2 inhibitor, and has shown some promise in stalling cSCC development over 24 months in high-risk immunosuppressed organ transplant recipients in a small study,<sup>168</sup> suggesting that further study is warranted.

Recently, the ornithine decarboxylase inhibitor  $\alpha$ -difluoromethylornithine (DFMO) has shown efficacy in reducing BCC incidence (0.40 events/patient-years vs. 0.28 events/patient-years;  $p=0.03$ ) in individuals with a prior history of NMSC, although no significant effects were noted on overall NMSC or cSCC incidence.<sup>169</sup> This trial was distinguished by its long period of intervention (4–5 years) and the simultaneous demonstration that the target, ornithine decarboxylase (ODC), was inhibited *in-vivo*, even though it could not be established as a surrogate endpoint. Importantly, long-term follow-up for the 5-year period following drug withdrawal was conducted, showing that the trend in lower NMSC rates persisted, though statistically insignificant.<sup>170</sup>

The recent approval of the systemic Hedgehog pathway inhibitor vismodegib has revolutionized the treatment of advanced and metastatic BCC.<sup>171, 172</sup> A randomized phase II trial examined both the efficacy in treatment and suppression of new BCCs in basal cell nevus syndrome patients, who develop hundreds of BCCs as a result of loss of function mutations in *PTCH1*. In addition to reducing the size of extant BCCs, vismodegib at 150 mg daily suppressed the emergence of new BCCs by a mean of 14.5-fold (2 vs. 29 BCCs per patient per year,  $p<0.001$ ) demonstrating a strong chemopreventive effect of this drug in this high-risk setting.<sup>171</sup>

**Melanoma:** Melanoma is the third-most common form of skin cancer, accounting for over 76,000 cancer diagnoses and 9,000 deaths per year in the United States.<sup>5</sup> Akin to AKs and cSCC, dysplastic nevi are regarded as potential precursor lesions to melanoma, although only about 25% of melanomas are histologically associated with nevi.<sup>173, 174</sup> Substantial work has been done attempting to advance the chemoprevention of melanoma, which could

ultimately have the greatest benefit in individuals with multiple dysplastic nevi and/or prior melanomas.<sup>175</sup>

Much of the investigational work in melanoma chemoprevention has been driven by epidemiological data. These data have suggested an association between the use of hypolipidemic agents (e.g., statins and fibrates) and lower melanoma incidence,<sup>176</sup> however early phase trials with lovastatin have failed to substantiate effects on melanoma or dysplastic nevi incidence or pathobiology.<sup>177</sup> There is conflicting epidemiological data on whether there is a protective effect of NSAID use on melanoma risk.<sup>175, 176</sup> The Women's Health Study, which used 100mg of aspirin every other day, showed no effect on melanoma risk, although this dose may have been too low.<sup>106</sup> Spurred by data on NSAIDs, oral sulindac was recently studied in a trial to assess whether relevant pharmacodynamic endpoints could be established short-term in atypical nevi. High levels of sulindac sulfone, a pro-apoptotic metabolite of sulindac, were achieved in benign nevi following 8 weeks of oral sulindac (150 mg b.i.d.), but this did not result in significant modulation of VEGFA levels or apoptosis in atypical nevi. The anti-inflammatory metabolite sulindac sulfide was not increased in nevi. While promising, these results show that the identification of better pharmacodynamic endpoints and optimal exposure times are needed and that definitive evidence of efficacy in preventing melanoma or nevus development or progression remain to be made.<sup>178</sup>

Currently, there are a handful of clinical melanoma prevention trials testing systemic sulindac, sulforaphane, vitamin D3, lovastatin, and N-acetylcysteine (Clinicaltrials.gov).<sup>176</sup> Of these, there are two ongoing phase III adjuvant studies of vitamin D3 supplementation, one of which is in resected stage II melanoma patients with primary endpoints of disease-free and overall survival following three years of treatment and two years of follow-up (NCT01264874) and the other of which is in patients following resection of their first cutaneous melanoma with a primary endpoint of disease-free survival during 3.5 years of follow-up from initial surgery (NCT01748448).

The combination of accessibility, preneoplastic intermediates, and the ability to use topical modalities continues to make skin a very fertile ground for the development of new cancer chemoprevention strategies. Although, high-risk groups are well-described for both NMSC and melanoma, suggesting ideal patient populations for testing interventions, studies in these group have been limited to small trials that have all demonstrated efficacy. Systemic acitretin in renal transplant recipients significantly lowered cSCC and AK incidences,<sup>162</sup> and topical T4N5 endonuclease reduced annual AK incidence (Rx = 8.2 vs. placebo = 25.9) and BCC incidence (Rx = 3.8 vs. placebo = 5.4) in xeroderma pigmentosum patients who lack nucleotide excision repair.<sup>179</sup> The phase III trial experience with vismodegib, performed in patients with an inherited predisposition to BCC,<sup>171</sup> emphasizes that agents useful for therapy may also be useful for chemoprevention. One major issue is that appropriate molecular surrogate endpoints that reflect drug action and biological activity must be developed. It is important to recognize, too, that testing and validation of chemoprevention strategies in skin cancers may inform efforts in other less accessible cancers that share molecular similarities (e.g. other SCC types).<sup>180-187</sup> Ideally, the confluence of compelling preclinical data, appropriate risk cohorts, as suggested by the success of trials in high-risk

groups,<sup>162, 171, 179</sup> adequate follow-up, and successful establishment of surrogate endpoints will drive trials that definitively establish efficacy. In this regard, NSAIDs and DFMO appear to be most promising in the near-term.

### Cancers with Phase III Trials, But No Approved Agents

**Head & Neck**—Multiple agents for oral cancer chemoprevention have been investigated over the past three decades, with retinoids as the most extensively studied drugs in this setting.<sup>188–192</sup> Unfortunately, these intensive investigations failed to develop a standard pharmacologic approach to prevent cancers in patients with oral premalignant lesions (OPL), either because of toxicity of the drugs and/or lack of long-term benefit. Nonetheless, the retinoid chemoprevention program has set the stage for translational research in this area. Correlative studies embedded in these clinical trials have led to the discovery of novel molecular markers of cancer risk, including cyclin D1,<sup>193</sup> RNA expression signatures,<sup>194</sup> EGFR overexpression/copy number gain,<sup>195</sup> and loss of heterozygosity (LOH) profiles.<sup>196</sup>

As of today, LOH represents the most robust marker of cancer risk in OPLs.<sup>196,197</sup> Building on this, the first personalized medicine cancer prevention trial based on molecular risk markers was completed: the Erlotinib Prevention of Oral Cancer (EPOC) study.<sup>198</sup> In this trial, patients with OPLs (with or without a prior history of invasive oral cancer) were first assessed for LOH at 3p14, 9p21, 4q, 8p, 11p, 13q, and 17p in premalignant lesions. High-risk patients (i.e., LOH +) were defined as those with LOH at 3p14 and/or 9p21 (and a prior history of oral cancer), or LOH at 3p14 and/or 9p21 plus at least one additional chromosomal site (if no prior history of oral cancer). All other patients were defined as low risk (LOH -). Low-risk patients were routinely followed in clinic without active intervention. High-risk patients (N=150) received erlotinib (150 mg p.o., q.d.) or placebo for 12 months and participated in follow-up for 24 months. The primary trial results reported at the 2014 ASCO Annual Meeting failed to demonstrate improved cancer-free survival with erlotinib over placebo (the primary endpoint).<sup>199</sup> There was a non-significant trend of benefit from erlotinib on cancer risk during the 12-month treatment period, which did not persist post-treatment. The most significant secondary finding was that EPOC patients who developed an erlotinib-related rash (grade 2) exhibited significantly increased cancer-free survival. While this represents the first prevention-based report of this phenomenon and of unclear biologic mechanism, the “rash-increased efficacy” finding is similar to that previously demonstrated in erlotinib-based lung and head and neck cancer therapeutic trials. Nonetheless, LOH has been shown to be a promising biomarker of cancer risk in patients with premalignant conditions (including Barrett’s esophagus) that can reliably stratify patients at high risk for future development of cancer. This is crucial for improving target intervention for high-risk patients while sparing the low-risk population from aggressive monitoring and treatment.

A distinct form of OPSCC is principally caused by human papillomavirus (HPV) and is increasing in incidence among men in the United States. From 1988 to 2004, the population-level incidence of HPV-positive OPSCC increased by 225% and is expected to exceed the yearly number of cervical cancers by the year 2020. Among men and women aged 14 to 69 years in the United States, the overall prevalence of oral HPV infection was 6.9%, and the prevalence was higher among men than among women. Oral sexual behavior was the

primary predictor of oral HPV16 infection; and once this behavior was adjusted for, age-cohort and race were no longer associated with oral HPV16 infection.<sup>200</sup> Although clear vaccine efficacy (VE) against oral HPV infections is not known, in a recent secondary analysis of a trial investigating VE of the bivalent HPV16/18 vaccine against cervical infections and lesions, Herrero et al. found that oral HPV prevalence four years after vaccination was significantly lower in the vaccine vs. control arm.<sup>201</sup> These results are promising for the prevention of both oral HPV infection and OPSCC.

Hong and colleagues reported that one year of high-dose 13-cis-retinoic acid (13-cRA) significantly reduces incidence of second primary tumors (SPTs) in curatively-treated stages I-IV head and neck squamous cell carcinoma (HNSCC) patients.<sup>202</sup> However, a subsequent large-scale NCI Intergroup phase III trial of low-dose 13-cRA involving 1,190 randomized stage-I/II HNSCC patients reported no difference in SPTs and/or recurrence rates between the 13-cRA and placebo arms.<sup>203</sup> To determine whether genetic background influences risk of SPT/recurrence and whether genetic markers could be used to predict patients most likely to benefit from 13-cRA, genetic variation was assessed by genotyping nearly 10,000 single nucleotide polymorphisms (SNPs) from cancer-related cellular pathways in 450 patients recruited to this trial.<sup>204</sup> The most significant findings were for the common genotype RXRA:rs3118570 located within an intron of the gene encoding the nuclear retinoid X receptor (RXRA), which participates in the transcriptional activation of retinoid-responsive genes. An increased risk of SPT/recurrence in the placebo arm was observed only in patients carrying this genotype: RXRA:rs3118570 identified a majority of patients (71%) at high risk of SPT/recurrence and therefore good candidates for intervention.<sup>204</sup> In addition to its prognostic value, RXRA:rs3118570 was predictive of 13-cRA efficacy, identifying this receptor as a target for chemoprevention with strong biological plausibility.<sup>204</sup> Though 13-cRA was once among the most promising agents for cancer chemoprevention, outcomes of phase III trials were disappointing.<sup>202, 203</sup> However, the important correlative work in this setting indicates the potential of genotyping and other translational studies to help personalize cancer prevention.

**Lung**—Despite the long-standing understanding of the pivotal role of tobacco in causing more than 80% of lung cancer<sup>205</sup> and the remarkable recent progress in identifying multiple targetable molecular driver mutations associated with lung carcinogenesis,<sup>206</sup> there are as yet no FDA-approved interventions to prevent lung cancer. The concept of prevention remains highly appealing since metastatic lung cancer is still incurable and many years of tobacco cessation are required to reduce (but not necessarily completely eliminate) lung cancer risk in former smokers.<sup>207</sup> The rationale for prevention is based on the recognition that the development of lung cancer is a lengthy process that occurs over extended time in response to tobacco carcinogen exposure, with the entire exposed epithelial surface being subject to damage and, thus becoming “at-risk”.<sup>208, 209</sup> However, even if effective agents are identified, there are many challenges to the unequivocal demonstration of their clinical efficacy, some of which are unique to lung cancer prevention. These include the difficulty in determining which smokers are truly likely to develop lung cancer, the relative inaccessibility of the lung to repeated biopsy sampling in order to gauge the effect of interventions, and the molecular heterogeneity of lung cancer, with identification of multiple

potential driver mutations that raises the possibility that different preventive interventions or combinations may be necessary for different molecular subtypes of lung cancer, as with breast cancer.<sup>206</sup>

Evidence-based clinical practice guidelines regarding chemoprevention of lung cancer have recently been published.<sup>210</sup> As summarized in Table 3, Phase III chemoprevention trials specifically designed to assess effects on lung cancer development have all shown either no efficacy or harm. These trials focused primarily on vitamins and micronutrients, based largely on epidemiologic evidence (such as in the case of  $\beta$ -carotene) or secondary endpoints from clinical trials (such as in the case of selenium) and a general perception of safety of dietary supplements.<sup>211–213</sup> The individual studies will not be discussed here. Instead, we will focus on the important lessons from these large trials.

The  $\alpha$ -Tocopherol,  $\beta$ -Carotene (ATBC) Study and the  $\beta$ -Carotene and Retinol Efficacy Trial (CARET) randomized 29,133 male smokers and 18,314 current or former smokers or asbestos-exposed workers, respectively, to regimens containing  $\beta$ -carotene and/or  $\alpha$ -tocopherol versus placebo (ATBC) or  $\beta$ -carotene and retinol versus placebo (CARET).<sup>211, 212</sup> Contrary to expectations, the risk of lung cancer was increased by 16% and 28%, respectively, in current but not former smokers. Consistent with the hypothesis of a negative interaction between  $\beta$ -carotene and smoking, this increased risk was not found in the Physicians' Health Study, which randomized many fewer current smokers (11% of 22,071 male physicians) to  $\beta$ -carotene and/or aspirin or placebo.<sup>214</sup> The  $\beta$ -carotene trials underscored the importance of having sufficient evidence from multiple diverse areas of investigation. The rationale for these trials was primarily based on epidemiologic observations, without the benefit of animal carcinogenesis modeling studies or a more mechanistic understanding of  $\beta$ -carotene actions.<sup>215</sup> There are inherent limitations to translating epidemiologic observations based on complex foods to clinical trials using a single nutrient given at a defined (usually pharmacologic replacement) dose for a finite period of time during the lengthy process of carcinogenesis.<sup>216</sup> Thus, the  $\beta$ -carotene experience emphasized the need for assessing multiple types of evidence when selecting a specific intervention strategy for phase III trials, even if this requires additional work to be done prior to trial launch.

The ECOG 5597 trial of selenium supplementation in patients with resected stage I non-small cell lung cancer similarly showed no benefit to the intervention and further underscored the need to have a sufficiently strong rationale composed of diverse indicators of efficacy.<sup>213</sup> This trial was based to a large extent on secondary endpoint analysis showing reduced lung cancer incidence after selenium supplementation in a prior skin cancer prevention trial,<sup>217</sup> but the populations between the two studies were significantly different in multiple respects, including baseline selenium levels. Long term follow-up of the skin cancer prevention trial, which only became available after the lung cancer trial was initiated, showed a trend toward benefit that was no longer statistically significant and was likely limited to the subgroup with the lowest baseline selenium levels.<sup>218</sup> Whether results observed in a population that never had prior tobacco-related malignancy can be extrapolated to a population of curatively-treated lung cancer survivors, who presumably have more severe tobacco-related damage, is also open to debate.

Taken together, the various phase III trials have served to energize the development of phase II preliminary efficacy trials that strive to add participant-level information on efficacy to the mechanistic, preclinical, and epidemiologic data that must be considered prior to launching phase III trials. Multiple studies examining the effects of interventions on lung cancer precursor lesions such as bronchial dysplasia, CT-detected indeterminate lung nodules, or putative intermediate endpoints such as proliferation index have been reported or are under way, as discussed below.<sup>210</sup> The goal of these trials is to develop the methodology for accurately assessing preliminary efficacy as well as testing the effects of the chemopreventive agents.

Among the most intriguing recent leads regarding lung cancer prevention is the analysis by Rothwell and colleagues, who performed a combined analysis of patient level data from multiple aspirin prevention studies and reported a 32% decrease in death from lung adenocarcinomas with aspirin use.<sup>219</sup> The decrease in lung cancer mortality was not dose dependent and only became significant after 5 or more years of treatment, suggesting an effect on cancer incidence and perhaps the earlier stages of carcinogenesis. Aspirin also reduced death from other adenocarcinomas, such as colorectal and esophageal cancers. Prevention of multiple chronic diseases with a drug that is cheap and whose side effect profile is well understood is very appealing. Several phase II trials exploring the effects of aspirin on biomarkers of lung carcinogenesis should help to further define the role of aspirin in lung cancer prevention (NCT02123849, NCT02135497). Other agents being studied in early phase clinical trials include iloprost, pioglitazone, green tea catechins, myo-inositol, erlotinib, isothiocyanates, and metformin.

Concomitant with identification of promising agents is the development of new clinical trials models to better assess efficacy. With the advent of helical CT comes an opportunity to examine the effect of interventions on the peripheral lung, where most adenocarcinomas arise. Data from a clinical trial of the inhaled steroid budesonide suggest that persistent non-solid lung nodules may be reasonable targets for phase II trials.<sup>220</sup> High-throughput technologies such as gene expression analysis of normal bronchial brushings are helping to identify critical pathways for lung cancer development, such as the phosphoinositide 3-kinase (PI3K) pathway that is frequently mutated in squamous cell carcinomas arising from tobacco damaged epithelia<sup>221</sup> and appears to be activated early (at the dysplasia stage) during lung carcinogenesis.<sup>222</sup> Reversion of this activation signature by the agent myo-inositol, corresponding to regression of dysplasia, in a small phase I trial<sup>222</sup> suggests possibilities for more personalized approaches to lung cancer chemoprevention. Combined with better identification of individuals who are most likely to develop cancer, such as on the basis of CT-detected lung nodules,<sup>223</sup> these novel approaches and new agents offer hope that disseminated lung cancer can, indeed, be prevented.

**Prostate**—The Prostate Cancer Prevention Trial (PCPT) tested finasteride (5mg q.d.), an inhibitor of type II 5 $\alpha$ -reductase, which converts testosterone to the more potent androgen dihydrotestosterone, for seven years (vs. placebo). PCPT randomized 18,882 men 55 years of age who had a normal digital rectal examination and prostate-specific antigen (PSA) level. Finasteride reduced the 7-year prostate cancer prevalence by 24.8%, but it also increased the rate of high-grade prostate cancer compared with placebo.<sup>224</sup> Consequently,

despite the fact that PCPT met its primary prostate cancer efficacy endpoint, the FDA did not approve finasteride use for the prevention of prostate cancer.<sup>225</sup> This trial and its subsequent FDA decision have generated much debate and follow-on analyses of the high-grade finding, including an extensive pathologic study<sup>226</sup> and complex statistical modeling.<sup>227</sup> Unfortunately, these efforts have failed to produce a clear resolution.

A recent long-term (18 year) follow-up report attempted to address the significance of the high-grade finding (e.g., finasteride-driven artifact vs. new finasteride-induced high-grade cancers) and found no significant between-group difference in the rates of overall survival or survival after the diagnosis of prostate cancer.<sup>228</sup> However, this analysis had only 6% power to identify an impact on overall survival given the small increase in the absolute number of men with high-grade disease in the finasteride arm and the relatively low impact of prostate cancer (even high-grade cancer) on mortality. Therefore, the low statistical power prevents the interpretation of these results regarding the high-grade controversy. Even if the increase in finasteride-induced high-grade disease is real, it is unlikely that the observed increase in high-grade disease significantly effects overall survival.<sup>228</sup>

The REDUCE trial tested the efficacy of another 5-alpha reductase inhibitor, dutasteride (0.5mg q.d.), in preventing prostate cancer in men with an elevated PSA (2.5–10 ng/mL) and a negative prostate biopsy. It demonstrated that men treated with dutasteride had a 23% overall reduction in diagnosis of biopsy-detected prostate cancer compared to placebo.<sup>229</sup> This reduction was due to decreased incidence of lower grade prostate cancer (Gleason score of 6). Unfortunately, as with finasteride, dutasteride was associated with increased risk of high-grade prostate cancer (Gleason score 8 to 10).

In 2001, the US National Cancer Institute initiated the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which tested whether selenium (Se; 200 µg/d from L-selenomethionine), vitamin E (400 IU q.d. of *all rac*- $\alpha$ -tocopheryl acetate) or both could reduce prostate cancer risk in over 35,000 men. Study supplementation stopped three years before the expected trial end date, because interim analyses showed very low likelihood of benefit with continued intervention. At that time, results demonstrated that vitamin E alone modestly increased prostate cancer risk (hazard ratio [HR]=1.13;  $p<0.06$ ).<sup>230</sup> Unfortunately, this increased risk of prostate cancer became statistically significant with additional follow-up (HR=1.17;  $p<0.008$ ).<sup>231</sup>

A recent follow-on analysis of SELECT investigated whether Se or vitamin E might benefit men with low baseline Se.<sup>232</sup> Contrary to this hypothesis, vitamin E supplementation (alone) increased risk of total prostate cancer by 63% ( $p=0.02$ ) in men with low baseline toenail Se (<40<sup>th</sup> percentile), and this effect was stronger for high-grade (111%;  $p=0.01$ ) versus low-grade (46%;  $p=0.09$ ) cancer. Among men with high baseline toenail Se (≥60<sup>th</sup> percentile), Se supplementation increased the risk of high-grade cancer by 91% ( $P=0.007$ ). While the results for vitamin E supplementation were unexpected, they are consistent with primary trial findings that vitamin E alone, but not vitamin E plus Se, increased risk. The findings from SELECT add to an already complex set of findings on the use of high-dose micronutrient supplementation for the primary prevention of cancer.

As it is unlikely that there will be another trial of high-dose Se or vitamin E supplementation for the primary prevention of prostate cancer, public health recommendations must be made without replication of these unexpected findings. Given the risks and lack of evidence of benefit for other diseases of equal or greater public health importance than prostate cancer, men >55 years of age should avoid supplementation with either vitamin E or Se at doses that exceed recommended dietary intakes.<sup>232</sup>

### **Cancers with Probable Risk Reduction Strategies Based on Treatment/Prevention of Infectious Agents**

**Liver/Hepatocellular**—Hepatitis B (HBV) and C (HCV) viruses represent significant risk factors for hepatocellular carcinoma (HCC), through the pathway of hepatitis and chronic liver disease. Primary prevention of HBV and HCV infections with vaccinations offers the possibility of also reducing HCC incidence and mortality. The Hepatitis B vaccine has been available since the 1980s and global infant vaccination efforts have dramatically reduced HBV carrier<sup>233</sup> and HCC incidence rates in endemic regions (e.g., Taiwan).<sup>234–236</sup> Perhaps most importantly, 30-year outcomes of the Taiwanese vaccination program reveal a 90% reduction in the mortality rate ratio of HCC between the 1977–1980 and 2001–2004 periods, demonstrating that prophylaxis against HBV infection prevents HCC.<sup>237</sup> While a vaccine for Hepatitis C is expected to have similar preventive effects for HCC, aspects unique to the hepatitis C virus challenge vaccine development.<sup>238</sup> Nevertheless, advances have been made in this area, and various vaccination strategies are currently being explored.<sup>239</sup> In an attempt to minimize HBV/HCV-related adverse health effects broadly, including HCC development, the Centers for Disease Control and Prevention currently recommends viral screening in asymptomatic or healthy high-risk populations, including one-time HCV screening in adults born between 1945 and 1965.<sup>240, 241</sup>

For treatment of viral hepatitis and downstream HCC prevention, anti-viral therapy (e.g., interferon and various nucleot(s)ide analogs, including ribavirin, lamivudine) may slow or block the progression of chronic liver disease. A recent compilation of anti-viral treatment trials identified five RCTs reporting on HCC incidence.<sup>13</sup> Two trials evaluated interferon- $\alpha$ 2a,<sup>242, 243</sup> one evaluated interferon- $\alpha$ 2b<sup>244</sup> and two evaluated lamivudine.<sup>245, 246</sup> The pooled relative risk from these five trials suggests a non-statistically significant 43% reduction in HCC risk following anti-viral treatment.<sup>13</sup> Multiple anti-viral HCV regimens are available, but RCT data examining the preventive efficacy of anti-virals on HCC incidence per se is currently lacking. However, observational data from 12 different studies totaling nearly 26,000 individuals suggests that a sustained virologic response after anti-viral therapy is associated with reduced HCC risk.<sup>247</sup> While increased understanding of the effect of anti-virals on clinical outcomes like HCC is needed for both HBV and HCV, the long-term follow-up of large numbers of individuals required for such studies has made this challenging.

**Gastric (Non-cardia)**—The gram-negative, microaerophilic bacterium *H. pylori* is associated with the majority of non-cardia gastric cancers (GCs) worldwide.<sup>248</sup>



Infection with *H. pylori* is typically treated with a course of “triple therapy” – a combination of antibiotics and proton pump inhibitors. Evidence from RCTs to support eradication of *H. pylori* as a strategy to prevent non-cardia GCs is emerging. A number of RCTs of various triple therapies have been conducted in individuals from regions with high rates of GC incidence.<sup>249–255</sup> However, results from these trials are conflicting and often non-significant. But most recently, a 15-year follow-up report from the Shandong Intervention Trial, released in 2012, demonstrated a statistically significant 39% reduction in GC incidence.<sup>256</sup> This is the first to demonstrate such a finding, and it is possibly due to the long term follow-up in that study.<sup>256</sup> A recent analysis of trial data by subgroup suggests that treatment benefits extend to older individuals, those with advanced baseline histopathology, and those with post-treatment infection.<sup>257</sup> While there is some emerging evidence, additional large-scale trials with extended follow-up may be required to see a significant protective effect of *H. pylori* eradication on gastric cancer incidence. Nevertheless, various groups, including the Asian-Pacific Gastric Cancer Consensus group, currently recommend screening and treatment for *H. pylori* in asymptomatic individuals from high-risk areas in order to reduce the burden of gastric cancer.<sup>258</sup>

In addition to *H. pylori* eradication with triple therapy, antioxidants and NSAIDs have also been tested for a chemopreventive benefit in RCTs. Trials of anti-oxidant supplements are based on the finding that diets high in fresh fruits and vegetables have been associated with reduced risk of GC. Vitamins C and E, selenium,  $\beta$ -carotene, and various combinations thereof, have been tested in a number of trials, including some of the previously mentioned trials examining *H. pylori* eradication.<sup>92, 93, 250, 251</sup> Results of these trials are conflicting and difficult to interpret. Consequently, data do not currently support the chemopreventive benefit of antioxidants in gastric cancer.

Regarding NSAIDs, there are some preclinical data to suggest that aspirin and other non-steroidal anti-inflammatories may have a protective effect against GC. To date, only one RCT has examined a COX-2 inhibitor specifically in relation to GC prevention. Wong, et al. randomized 1,024 *H. pylori*-infected patients with advanced gastric lesions to anti-*H. pylori* treatment for 7 days, celecoxib for 24 months, both, or neither.<sup>259</sup> Findings demonstrated that treatment with either celecoxib or anti-*H. pylori* treatment alone had beneficial effects on lesion regression; but that anti-*H. pylori* treatment followed by celecoxib was not statistically significantly better than placebo.<sup>259</sup> In addition to celecoxib, aspirin as a GC preventive strategy has been examined in a meta-analysis of individual-level patient data from cardiovascular disease RCTs which reported deaths from various cancers.<sup>219</sup> Results showed a significant protective effect (HR: 0.42; 95% CI: 0.23–0.79) of aspirin on GC mortality for those treated >10 years.<sup>219</sup>

In summary, there is emerging evidence that eradication of *H. pylori* with triple therapy may prevent non-cardia GC, and that NSAIDs may offer a true chemopreventive strategy for GC. Additional high-quality phase III trials are required of each potential strategy to confirm the suggested protective effects. Two phase III trials are currently on-going in Korea. NCT02112214 is testing a 10-day bismuth-based course of quadruple therapy in the general population with a primary outcome of GC incidence, while NCT01678027 is testing the

ability of LAC (lansoprazole, amoxicillin, clarithromycin) triple therapy to reduce risk of gastric cancer in first-degree family members of GC patients.

The role of *H. pylori* in cardia gastric cancers is unclear. Results of observational studies are mixed, with those in Asian populations generally suggesting that *H. pylori* increases the risk of cardia cancer<sup>260</sup> and those in Western populations suggesting a protective or null association.<sup>261,262,263</sup> Some have suggested that *H. pylori* is a risk factor for adenocarcinoma throughout the stomach, including cardia cancers, and that risk estimates in Western populations may be influenced by the high prevalence of gastroesophageal reflux disease (GERD) in those countries and an over representation of misclassified GERD associated lower esophageal malignancies.<sup>260</sup> A 2011 meta-analysis of 34 studies suggests no overall association between *H. pylori* and gastric cardia cancer, but an increased risk in high-risk (i.e. Asian) settings and a suggestive inverse association in low-risk (i.e. Western populations) settings.<sup>264</sup> The authors suggest these results support the hypothesis of a mixed distribution of etiologically distinct types of cardia cancer, where one type occurs through *H. pylori*-associated gastric atrophy, and the other occurring in non-atrophic gastric mucosa and driven by damage from acid/bile in the distal esophagus, similar to esophageal adenocarcinoma.<sup>264</sup> Further prospective, long-term studies that carefully take into account the presence or absence of gastric atrophy and reflux symptoms will be needed to clarify the exact role of *H. pylori* in gastric cardia cancers.

## Future Directions in Chemoprevention

Although chemoprevention as a strategy to reduce the burden of cancer has been challenged by some,<sup>265</sup> recent genomic data highlighting the extreme genetic complexity found in advanced cancers questions a continued emphasis on the development of later-stage therapies versus strategies targeting earlier stages of carcinogenesis. Nevertheless, in order for chemoprevention to be fully realized as an effective strategy, a number of challenges to the field must be addressed.

A better understanding of the premalignant genome and/or premalignant lesions will allow for the identification of key molecular determinants of pre-cancer development; and, hence, the development of safe and effective agents to target these determinants and reverse, inhibit, or halt further progression to cancer. The pancreas represents an organ where a more comprehensive understanding of the molecular changes underlying pancreatic intraepithelial neoplastic lesions should help in the identification of potential chemopreventive targets and/or biomarkers. Agents that are multifunctional in nature (e.g., triterpenoids) and strategies involving intermittent dosing and/or drug combinations should be a high-priority for testing in clinical trials.<sup>137, 266, 267</sup> Recent experience with preventive combinations offer great hope,<sup>137</sup> and some studies suggest that some agents used in cancer treatment (e.g., tamoxifen, AIs, EGFR inhibitors) may be just as useful, if not more so, when applied earlier in a preventive context. Embedding prevention endpoints in the therapeutic clinical trials of the future could facilitate the identification of such additional agents. And trials based on cohorts at high-risk of cancer due to inherited germline mutations (e.g., BRCA carriers) or specific exposure histories (e.g., former smokers), offer a number of advantages over average-risk cohorts, including more power over shorter time frames and reduced cost.

Smaller, cheaper and faster trials will facilitate accelerated development of promising chemopreventive agents. Finally, integrative risk assessment and long-term outcome determinations across multiple diseases (e.g. considering risks of, and outcomes across, cancer, cardiovascular disease and diabetes together), with periodic collection of biospecimens offering improved mechanistic insights into efficacy and/or safety, may help tip the risk:benefit ratio in favor of the use of a particular chemopreventive agent. This point is succinctly illustrated by the very recent publication of extended long-term follow-up (median of 16 years) data from the IBIS-I trial, which showed a greatly improved benefit-to-harm ratio for tamoxifen.<sup>33</sup> One can only imagine the complexity and relevance of such a consideration applied to an agent like aspirin which reduces the risk of CVD events and seems to reduce the risk of gastric, esophageal and colorectal cancers, but increases the risk of bleeding and upper gastrointestinal ulcers. Yet, this is the dilemma facing physicians daily. As chemoprevention evolves, the optimal approach to cancer is likely to transition from one based solely upon treatment to one based upon prevention, including lifestyle modifications, risk-reducing pharmacologic agents, and early detection, as is neatly illustrated in the evolving management of cardiovascular disease over the last two to three decades.

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**Table 1**

FDA Approved Agents for Treatment of Precancerous Lesions or Cancer Risk Reduction in Indicated Cohorts

Agent	Targeted Cohort in Indication*	FDA Indication*
Tamoxifen	Women with DCIS following breast surgery and radiation	Reduction in risk of invasive breast cancer
Tamoxifen	Women at high risk for breast cancer ("high risk" defined as women at least 35 years of age with a 5-year predicted risk of breast cancer $\geq$ 1.67%, as calculated by the Gail Model)	Reduction in incidence of breast cancer
Raloxifene	Postmenopausal women at high risk for invasive breast cancer ("high risk" defined as at least one breast biopsy showing lobular carcinoma in situ or atypical hyperplasia, one or more first-degree relatives with breast cancer, or a 5-year predicted risk of breast cancer $\geq$ 1.66% (based on the modified Gail model).	Reduction in risk of invasive breast cancer
HPV Vaccine (Cervarix)	Females 9 through 25 years of age	Prevention of the following diseases caused by oncogenic human papillomavirus (HPV) types 16 and 18: <ul style="list-style-type: none"> <li>• Cervical cancer</li> <li>• Cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma in situ</li> <li>• Cervical intraepithelial neoplasia (CIN) grade 1</li> </ul>
HPV Vaccine (Gardasil 9)	Girls and women 9 through 26 years of age	Prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine: <ul style="list-style-type: none"> <li>• Cervical, vulvar, vaginal, and anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, &amp; 58</li> <li>• Genital warts caused by HPV types 6 and 11</li> </ul> And the following precancerous or dysplastic lesions caused by HPV types 6,11, 16, 18, 31, 33, 45, 52, and 58: <ul style="list-style-type: none"> <li>• Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma in situ (AIS)</li> <li>• Cervical intraepithelial neoplasia (CIN) grade 1</li> <li>• Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3</li> <li>• Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3</li> <li>• Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3</li> </ul>
HPV Vaccine (Gardasil 9)	Boys and men 9 through 15 years of age	Prevention of the following diseases caused by HPV types included in the vaccine: <ul style="list-style-type: none"> <li>• Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, &amp; 58</li> <li>• Genital warts caused by HPV types 6 and 11</li> </ul> And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, & 58: <ul style="list-style-type: none"> <li>• Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3</li> </ul>

Agent	Targeted Cohort in Indication *	FDA Indication *
Photodynamic Therapy (PDT) with Photofrin	Males and females with high-grade dysplasia in Barrett's esophagus	Ablation of high-grade dysplasia (HGD) in Barrett's esophagus (BE) patients who do not undergo esophagectomy
Celecoxib **	Males and females 18 years old with familial adenomatous polyposis (FAP)	Reduction in the number of adenomatous colorectal polyps in FAP, as an adjunct to usual care (e.g., endoscopic surveillance, surgery)
Bacillus-Calmette-Guerin (BCG)	Males and females with carcinoma in situ (CIS) of the urinary bladder	Intravesical use in the treatment and prophylaxis of carcinoma <i>in situ</i> (CIS) of the urinary bladder and for the prophylaxis of primary or recurrent stage Ta and/or T1 papillary tumors following transurethral resection (TUR)
Valrubicin	Males and females with Bacillus-Calmette-Guerin (BCG)-refractory carcinoma in situ (CIS)	Intravesical therapy of BCG-refractory carcinoma <i>in situ</i> (CIS) of the urinary bladder in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality
Fluorouracil	Males and females with multiple actinic or solar keratoses	Topical treatment of multiple actinic or solar keratoses
Diclofenac sodium	Males and females with actinic keratoses	Topical treatment of actinic keratoses
Photodynamic Therapy (PDT) with 5-aminolevulinic acid	Males and females with actinic keratoses of the face or scalp	Topical treatment of minimally to moderately thick actinic keratoses of the face or scalp.
Masoprocol ***	Males and females with actinic (solar) keratoses	Topical treatment of actinic keratoses
Imiquimod	Immunocompetent adults	Topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp
Ingenol mebutate	Males and females with actinic keratoses on the face, scalp, trunk and extremities	Topical treatment of actinic keratoses

\* According to FDA product label

\*\* FDA labeling voluntarily withdrawn by Pfizer, February 2011

\*\*\* Withdrawn from US market, June 1996

**Table 2**

Interventions that Likely Reduce Cancer Risk through Treatment or Prevention of Microbial and Parasitic Infections and Diseases

<b>Infectious Organism</b>	<b>Associated Cancer</b>	<b>Intervention</b>
Hepatitis B virus	Hepatocellular Carcinoma	Hepatitis B vaccine, Interferon therapy, nucleoside analogues <sup>13</sup>
Hepatitis C virus	Hepatocellular Carcinoma	Interferon therapy, nucleoside analogues <sup>14</sup>
Human Immunodeficiency Virus (HIV)	Kaposi's Sarcoma & Non-Hodgkin's Lymphoma	Anti-Retro Viral Therapies <sup>15</sup> (ARTs)
Helicobacter Pylori	Gastric/Stomach Cancer	Antibiotics <sup>16</sup> – “Triple/Quadruple Therapy”
Schistosomiasis	Bladder Cancer	Antischistosomal <sup>17</sup> – Praziquantel and Metrifonate

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**Table 3**

Organ System	Cohort	Sample Size	Intervention × Duration	Primary Efficacy Measure(s)	Effect of Intervention on Risk	Author & Year of Publication(s)
Breast	Women with resected stage I cancer or DCIS	2,972	Femnetinide 200 mg/d vs. placebo × 5 yrs	Contralateral breast cancer incidence HR = 0.92 (95% CI = 0.66–1.29); Ipsilateral breast cancer recurrence HR = 0.83 (95% CI = 0.64–1.09)	Null	Veronesi 1996, 1999
	Women with increased risk of breast cancer (Gail model) (NSABP-P1/BCPT)	13,388	Tamoxifen 20 mg/d vs. placebo × 5 yrs	Invasive breast cancer incidence RR = 0.51, p<0.00001; Noninvasive breast cancer incidence RR = 0.50, p<0.002 Invasive breast cancer incidence RR = 0.57 (95% CI = 0.46 – 0.70) Noninvasive breast cancer incidence RR = 0.63 (95% CI = 0.45 – 0.89).	Effective	Fisher 1998 Fisher 2005
	Women with family history of breast cancer (Royal Marsden)	2,471	Tamoxifen 20 mg/d vs. placebo × median of 70 mos	Primary cancer incidence RR = 1.06 (95% CI = 0.7–1.7), p=0.8 20-yr. Follow-up: - Invasive Breast Cancer HR = 0.78 (95% CI = 0.58 – 1.04; P = 0.1) - ER+ Breast Cancer HR = 0.61 (95% CI = 0.43 – 0.86; P = .005) <i>secondary planned analysis</i>	Null (Effective for ER+ at 20-yr Follow-up)	Powles 1998 Powles 2007
	Women with normal risk, post-hysterectomy	5,408	Tamoxifen 20 mg/d vs. placebo × 5 yrs	Primary cancer incidence – no significant effect Secondary analyses of: - High-risk subset – reduced, p=0.003; - Low risk subset – no effect, p=0.89 Breast cancer incidence RR = 0.84 (95% CI = 0.60 to 1.17) -High-risk subset RR = 0.24 (95% CI = 0.10 to 0.59)	Null (Effective in High-risk subset)	Veronesi 1998 Veronesi 2007
	Women with increased risk of breast cancer (> 2 fold relative risk) (IBIS-1)	7,139	Tamoxifen 20 mg/d vs. placebo × 5 yrs	Primary cancer incidence risk reduction = 32% (95% CI = 8–50), p = 0.013 Breast cancer incidence RR = 0.73 (95% CI = 0.58 to 0.91), P = 0.004	Effective	IBIS investigators 2002 Cuzick 2007

Organ System	Cohort	Sample Size	Intervention × Duration	Primary Efficacy Measure(s)	Effect of Intervention on Risk	Author & Year of Publication(s)
	High-risk, postmenopausal women > 35 years of age (NSABP-P2/STAR)	19,747	Tamoxifen 20 mg/d or raloxifene 60 mg/d × 5 yrs	Invasive breast cancer RR = 1.02 (95% CI = 0.82–1.28) Noninvasive breast cancer RR = 1.40 (95% CI = 0.98–2.00) Invasive breast cancer RR = 1.24 (95% CI = 1.05–1.47) Noninvasive breast cancer RR = 1.22 (95% CI = 0.95–1.59)	Raloxifene as effective as Tamoxifen	Vogel 2006 Vogel 2010
	Postmenopausal women with low bone mineral density (BMD) < 80 years of age (MORE)	7,705	Raloxifene 60 or 120 mg/d or placebo × 4 yrs	<b>3-year results:</b> Breast cancer incidence RR = 0.24 (95% CI = 0.13–0.44), P < 0.001 ER+ breast cancer RR = 0.10 (95% CI = 0.04–0.24) ER- breast cancer RR = 0.88 (95% CI = 0.26–3.0). <b>4-year results:</b> Invasive breast cancer RR = 0.28 (95% CI = 0.17–0.46) ER+ breast cancer RR = 0.16 (95% CI = 0.09–0.30) ER- breast cancer RR = 1.13 (95% CI = 0.35–3.66)	Effective (ER+ only)	Cummings 1999 Caulley 2001
	Postmenopausal women with low bone mineral density (BMD) re-consented from MORE trial < 80 years of age (CORE)	4,011	Raloxifene 60 mg/d or placebo × an additional 4 yrs after 4 yrs of raloxifene on MORE trial	Incidence of invasive breast cancer HR = 0.41 (95% CI = 0.24 to 0.71) ER+ invasive breast cancer HR = 0.34 (95% CI = 0.18 to 0.66) No difference between the two groups in incidence of ER- negative invasive breast cancer (P = .86) Over 8 yrs of MORE + CORE: Incidence of invasive breast cancer HR = 0.34 (95% CI = 0.22 to 0.50) ER+ invasive breast cancer HR = 0.24 (95% CI = 0.15 to 0.40)	Effective (ER+ only)	Martino 2004
	Postmenopausal women with CHD > 35 years of age (RUTH)	10,101	Raloxifene 60 mg/d or placebo × median of 5.6 yrs	Invasive breast cancer HR = 0.56 (95% CI = 0.38 to 0.83)	Effective	Barrett-Connor 2006
	Women with low BMD 59–80 years of age (PEARL)	8,556	Lasoxifene 0.25 mg or 0.5 mg/d or placebo × 5 yrs	At 0.5mg/d dose: Total breast cancer HR = 0.21 (95% CI = 0.08 to 0.55)	Effective	LaCroix 2010 Cummings 2010

Organ System	Cohort	Sample Size	Intervention × Duration	Primary Efficacy Measure(s)	Effect of Intervention on Risk	Author & Year of Publication(s)
	Women with low BMD (GENERATIONS)	9,354	Arzoxifene 20 mg/d or placebo × 4 yrs	ER+ invasive breast cancer HR = 0.17 (95% CI = 0.05 to 0.57). At 0.5mg/d dose: ER+ breast cancer HR = 0.19 (95% CI = 0.07 – 0.56)	Effective	Cummings 2011 Powles 2012
	Postmenopausal women aged 40–70 at increased risk of breast cancer (IBIS-II)	3,864	Anastrozole 1 mg/d vs. placebo × 5 yrs	Histologically confirmed breast cancer HR = 0.47 (95% CI 0.32–0.68), P<0.0001	Effective	Cuzick 2008 Cuzick 2014
	Postmenopausal women aged 55 or older at increased risk (NCIC-MAP.3)	4,560	Exemestane 25 mg/d vs. placebo × 5 yrs	Invasive breast cancer HR = 0.35 (95% CI = 0.18 to 0.70), P=0.002 Invasive + noninvasive (DCIS) breast cancers HR = 0.47 (95% CI = 0.27 to 0.79), P=0.004	Effective	Goss 2011
<b>Cervix</b>	Women with CIN II and III	301	Cervical caps with all-trans-retinoic acid 1 ml of 0.372% vs. placebo × 6 mos (periodically)	CIN-II complete histologic regression – 59% increase, p = 0.041; CIN-III regression – no difference	Effective (borderline)	Meyskens 1994
	Women with prevalent koilocytic atypia, CIN I or II	331	Folic acid 5 mg/d vs. placebo × 6 mos	Cytologic or colposcopic CIN – no significant improvement	Null	Childers 1995
	Women 16–23 years old	2,392	HPV-16 virus-like particle vaccine 40 mcg/dose vs. placebo × 3 with 17.4 mos follow-up	HPV-16 related CIN incidence – Rx vs. placebo = 0 vs. 9 cases, p<0.001	Effective	Koutsky 2002
	Women with CIN II or III	114	9-cis-retinoic acid 25 mg/d vs. 50 mg/d vs. placebo × 12 wks	CIN Regression rates – placebo = 32%; low-dose = 32%; high-dose = 36%, No significant differences	Null	Alvarez 2003
	Women with high grade cervical squamous intraepithelial neoplasia	175	Cervical caps with sponge of all-trans-retinoic acid 0.16% vs. 0.28% vs. 0.37% vs.	CIN complete regression rates: Placebo = 47%; low-dose = 56%;	Null	Ruffin 2004

Organ System	Cohort	Sample Size	Intervention × Duration	Primary Efficacy Measure(s)	Effect of Intervention on Risk	Author & Year of Publication(s)
	Women not previously infected with HPV-16 or -18	12,167	placebo × 4d with outcomes at 12 wks HPV-6/11/16/18 vaccine vs. placebo (3 doses of vaccine at day 0, 2 mo., 6mo.) with average of 3 yrs of follow-up after the 1 <sup>st</sup> dose	moderate-dose = 50%; high dose = 40% No significant differences, p=0.28 HPV 16/18-related grade 2 or 3 CIN lesions, adenocarcinoma, or HPV-16/18-related cervical cancer Vaccine efficacy: 98% (95% CI: 86–100)	Effective	FUTURE II Study Group 2007
Esophagus	Residents of Huixian, China (with an assumed high prevalence of dysplasia or cancer)	610	Retinol 50,000 IU/d + riboflavin 200 mg/d + zinc 50 mg/d vs. placebo × 13.5 mos	OR of a normal esophagus at the conclusion of treatment = 0.85 (95% CI = 0.60–1.21)	Null	Munoz 1985
	Residents of Linxian, China 40–69 years old at high risk for gastroesophageal cancers	29,584	Complex factorial design with 4 arms: - retinol + zinc - riboflavin + niacin - vitamin C + molybdenum - BC + vitamin E + selenium × 1–5 yrs	Esophageal cancer incidence RR = 0.86 (95% CI = 0.74–1.01) with riboflavin + niacin Esophageal cancer mortality RR = 0.90 (95% CI = 0.73–1.11) with riboflavin + niacin Esophageal cancer mortality RR = 0.96 (95% CI = 0.78–1.18) with BC + vitamin + selenium <i>15-yr. follow-up</i> Esophageal cancer mortality HR = 0.93 (95% CI = 0.84 to 1.02) with riboflavin + niacin Esophageal cancer mortality HR (< 55) = 0.83 (95% CI = 0.71 to 0.98 with BC + vitamin E + selenium Esophageal cancer mortality HR (age 55) = 1.14 (95% CI = 1.00 to 1.30) with BC + vitamin E + selenium	Null (BC + vitamin E + selenium effective in reducing esophageal cancer mortality in those under age 55 at 15-yr Follow-up)	Blot 1993 Qiao 2009
	Residents of Linxian, China with esophageal dysplasia	3,318	Multivitamin supplement (containing 14 vitamins and 12 minerals) vs. placebo × 5.25 yrs	RR of esophageal/gastric cardia death = 0.92 (95% CI = 0.67–1.28) 26-yr follow-up: HR of esophageal/cardia death = 0.95 (95% CI = 0.83–1.10) HR of total cancer deaths = 0.97 (95% CI = 0.85–1.10) HR of total deaths = 0.98 (95% CI = 0.90–1.06)	Null	Li 1993 Wang 2013
	Residents of Linxian, China with mild to moderate esophageal dysplasia	238	Selenomethionine 200µg daily and/or celecoxib	Selenomethionine: Trend towards increased dysplasia regression (43% vs 32%) &	Null (Selenomethionine effective on dysplasia)	Limburg 2005



Organ System	Cohort	Sample Size	Intervention × Duration	Primary Efficacy Measure(s)	Effect of Intervention on Risk	Author & Year of Publication(s)
	High-grade Barrett's dysplasia	208	200mg twice daily × 10 mos	decreased dysplasia progression (14% vs 19%); P=0.08 Significant effect on dysplasia grade in those with mild dysplasia (P=0.02), but not in those with moderate (p=1.00) Celecoxib: no effect on dysplasia grade overall (P=0.78) or by baseline histologic grade	grade in those with low-grade dysplasia	Product label 2003
	Patients with Barrett's esophagus and low- or high-grade dysplasia	100	Forfimer sodium 2mg/kg (followed by photodynamic light therapy) + omeprazole vs. omeprazole × 2-3.6 yrs  Celecoxib 200 mg twice daily × 48 wks	CR3 or greater (major response) in 77% vs. 39%, p<0.0001; CR1 (complete response) in 52% vs. 7%, p<0.0001; cancer-free at 24 mos = 83% vs. 53%, p=0.0014  No significant difference in proportion of biopsy samples with dysplasia or cancer in either the low-grade (median change with celecoxib = -0.09, interquartile range [IQR] = -0.32 to 0.14 and with placebo = -0.07, IQR = -0.26 to 0.12; P = .64) or high-grade (median change with celecoxib = 0.12, IQR = -0.31 to 0.55, and with placebo = 0.02, IQR = -0.24 to 0.28; P = .88) groups.	Effective	Heath 2007#
<b>Colorectum</b>	<b>NSAIDs</b>					
	FAP with prevalent adenomas	10 (cross-over design)	Sulindac 300 mg/d vs. placebo × 4 mos	Complete or near complete CR adenoma regression Sulindac - 9 vs. placebo - 0 (increase in 5, stable disease in 2, relative reduction in 2), p < 0.01	Effective	Labayle 1991
	FAP with prevalent adenomas	22	Sulindac 150 mg BID vs. placebo × 9 mos	CR polyp number - 56% reduction, p=0.014; CR polyp diameter - 65% reduction, p<0.001	Effective	Giardello 1993
	FAP with prevalent adenomas	24	Sulindac vs. placebo x 6 mos	CR polyp number - significantly reduced, p=0.01; Duodenal polyp number - trend toward reduction, p=0.12	Effective	Nugent 1993

Organ System	Cohort	Sample Size	Intervention × Duration	Primary Efficacy Measure(s)	Effect of Intervention on Risk	Author & Year of Publication(s)
	U.S. male physicians	22,071	Aspirin 325 mg QOD vs. BC 50 mg QOD vs. both vs. neither × 5 yrs	Primary CRC incidence RR = 1.15 (95% CI = 0.80–1.65); In situ cancer/polyp incidence RR = 0.86 (95% CI = 0.68–1.10) CRC Incidence after 12 yr. follow-up: - RR = 1.03 (95% CI = 0.83 to 1.28)	Null	Gann 1993 Sturmer 1998
	FAP with prevalent adenomas	77	Celecoxib 200 BID vs. 400 BID vs. placebo × 6 mos	Mean number of adenomas – 28% reduction, p=0.003; Polyp burden – 30.7% * reduction, p=0.001	Effective	Steinbach 2000
	Genotype + phenotype – FAP patients 8–25 years old	41	Sulindac 75–150 mg BID vs. placebo × 48 mos	Adenoma incidence – sulindac = 43% vs. placebo = 55%, p=0.54; mean number or size of adenomas – no significant differences	Null	Giardiello 2002
	Recent resected adenoma	1,121	Aspirin 81 mg/d vs. 325 mg/d vs. placebo × yrs	Adenoma recurrence - 81 mg RR = 0.81 (95% CI = 0.69–0.96); - 325 mg RR = 0.96 (95% CI = 0.81–1.13); Secondary analysis for advanced adenoma - 81 mg RR = 0.59 (95% CI = 0.38–0.92); - 325 mg RR = 0.83 (95% CI = 0.55–1.23)	Effective (low-dose only)	Baron 2003
	Resected early stage colorectal cancer	635	Aspirin 325 mg/d vs. placebo × 3 yrs	Recurrent adenoma RR = 0.65 (95% CI = 0.46–0.91); Time to first adenoma prolonged HR = 0.64 * (95% CI = 0.43–0.94), p = 0.022	Effective	Sandler 2003
	Recent resected adenoma	272	Lysine acetylsalicylate 160–300 mg/d vs. placebo × 1 yr Lysine acetylsalicylate 160–300 mg/d vs. placebo × 4 yrs	Adenoma recurrence RR = 0.73 (95% CI = 0.52–1.04), p = 0.08; Secondary analysis of large adenomas – 83% reduction, p=0.01 4-yr Follow-up Analysis: - Proportion of pts with at least 1 recurrent adenoma: 41% in aspirin vs. 40% in placebo, NS - Polyp burden: 3.1±5.8mm vs. 3.4±6.2mm, NS	Null (Effective in secondary analysis of large adenomas)	Benamouzig 2003 Benamouzig 2012

Organ System	Cohort	Sample Size	Intervention × Duration	Primary Efficacy Measure(s)	Effect of Intervention on Risk	Author & Year of Publication(s)
	U.S. Women aged 45, initially without hx of cancer, CVD, or other major chronic illness	39,876	Aspirin 325 mg QOD vs. placebo × 5 yrs	- Proportion of pts with at least 1 advanced recurrent adenoma: 10% vs. 7%, NS CRC Incidence : - RR = 0.97 (95% CI = 0.77–1.24) CRC Incidence after overall 18 yr. follow-up: - RR = 0.80 (95% CI = 0.67–0.97)	Null (Effective at 18-yr Follow-up)	Cook 2005 Cook 2013
	Recent resected adenoma	1,561	Celecoxib, single 400-mg dose/d vs. placebo × 3 yrs	Adenoma Recurrence: RR, 0.64 (0.56–0.75), P<0.001 Advanced Adenomas: RR, 0.49 (0.33–0.73), P<0.001	Effective	Arber 2006
	Recent resected adenoma	2,035	Celecoxib, 400 mg/d or 800 mg/d vs. placebo × 3 yrs	Recurrence of 1 or More Adenomas: 400 mg/d – RR, 0.67 (0.59–0.77), P<0.001 800 mg/d – RR, 0.55 (0.48–0.64), P<0.001 *Celecoxib significantly & dose-dependently associated with increased risk of CVD events	Effective (but increased risk of CVD events)	Bertagnoli 2006
	Meta-analysis of cardiovascular trials reporting cancer endpoints	7,588	UK-TIA: Aspirin 300–500 mg/d vs. placebo × 1–7 yrs British Doctors' Aspirin Trial: Aspirin 300–1500 mg/d vs. no aspirin × 5–6 yrs	CRC Incidence: - HR = 0.74 (95% CI = 0.56–0.97) - Effect seen after 10 yr latency	Effective (after 10-yr latency)	Flossman 2007
	Recent resected adenoma	375	Oral difluoromethylornithine (DFMO) 500 mg and sulindac 150 mg once daily or matched placebo × 36 mos	Recurrence of 1 or more adenomas: RR, 0.30 (0.18–0.49), P <0.001 Advanced adenomas: RR, 0.085 (0.011–0.65), P <0.001 Multiple adenomas: RR, 0.055 (0.0075–0.41), P < 0.001	Effective	Meyskens 2008
	Recent resected adenoma	939	Aspirin 300 mg/d and folate supplements 0.5 mg/d vs. placebo in 2×2 factorial design × 3 yrs	Adenoma recurrence RR = 0.79 (95% CI = 0.63–0.99) Advanced adenoma RR = 0.63 (95% CI = 0.43–0.91)	Effective	Logan 2008

Organ System	Cohort	Sample Size	Intervention × Duration	Primary Efficacy Measure(s)	Effect of Intervention on Risk	Author & Year of Publication(s)
	Meta-analysis of cardiovascular trials reporting cancer endpoints	14,033	Aspirin (75–120mg/d) vs. control × 6 yrs. (mean duration of treatment)	CRC incidence: HR = 0.76; (95% CI = 0.60–0.96), <i>P</i> = 0.02 CRC mortality: HR = (0.65; 95% CI = 0.48–0.88), <i>P</i> = 0.005	Effective	Rothwell 2010
	FAP patients, ages 10–21 (CAPP-1)	206	Aspirin 600 mg/d and/or resistant starch (30 g/d) vs. placebo × 1–12 yrs	Polyp Count: aspirin – RR, 0.77 (0.54–1.10) Size of Largest Observed Polyp: Mean size = 3.0mm in aspirin-treated group v 6.0mm in placebo group, <i>P</i> = 0.02	Null (Effective for size of largest observed polyp)	Burn 2011
	Carriers of Lynch Syndrome (CAPP-2)	937	600 mg aspirin or aspirin placebo or 30 g resistant starch or starch placebo, for up to 4 yrs	Time to First CRC: HR, 0.63 (0.35–1.13), <i>P</i> = 0.12 For those completing 2yrs of intervention: HR = 0.41 (95% CI = 0.19–0.86), <i>P</i> = 0.02; IRR, 0.37 (95% CI = 0.18–0.78), <i>P</i> = 0.008	Null (Effective for those completing 2 yrs of intervention)	Burn 2011
	<b>Hormone Replacement Therapy</b>					
	Post-menopausal women with coronary artery disease	2,763	0.625 mg/d conjugated estrogens + 2.5 mg/d medroxyprogesterone acetate vs. placebo × 4 yrs	CRC incidence: no significant difference between intervention and placebo groups: HR (unadjusted intention-to-treat), 0.81 (0.46–1.45) HR (adjusted, as-treated), 0.58 (0.25–1.35)	Null	Hulley 2002
	Healthy post-menopausal women	16,608	0.625mg/d conjugated equine estrogen + 2.5mg/d medroxyprogesterone acetate vs. placebo × 5.2 yrs	CRC incidence: RR, 0.63 (0.43–0.92) CRC stage at diagnosis: rate of regional or metastatic disease in hormone group (76.2%) v placebo (48.5%), <i>P</i> = 0.004	Effective	Rossouw 2002 Chlebowski 2004
	Health post-menopausal women with hysterectomy	10,738	Conjugated equine estrogen 0.625mg/d vs. placebo × 7.1 yrs	CRC incidence: 1.08 (0.75–1.55) Survival Following CRC Diagnosis: 1.34 (0.58–3.19)	Null	Anderson 2004 Ritenbaugh 2008
	<b>Micronutrients/Dietary Agents</b>					
	Recent resected adenoma	864	β-carotene 25mg/d vs. vitamin C 1 gm/d + vitamin E 400 mg/d vs. both vs. placebo × 4 yrs	Adenoma recurrence: - BC RR = 1.01 (95% CI = 0.85–1.20);	Null	Greenberg 1994

Organ System	Cohort	Sample Size	Intervention × Duration	Primary Efficacy Measure(s)	Effect of Intervention on Risk	Author & Year of Publication(s)
	Recent resected adenoma	424	Low dietary fat (25% of calories) vs. 25 gm/d wheat bran vs. carotene 20 mg/d vs. combinations vs. placebo × yrs	- Vit C + E RR = 1.08 (95% CI = 0.91–1.29) Adenoma recurrence: No significant effect with any of the interventions; Secondary analysis of large adenoma recurrence: low fat + wheat bran combination reduced recurrence, p=0.03	Null (Low fat + wheat bran effective in secondary analysis)	MacLennan 1995
	Patients with prior skin cancer	1,312	Selenium 200µg/d vs. placebo × 6.4 yrs	CRC incidence: RR, 0.42 (0.18–0.95), P=0.03	Effective	Clark 1996
	Recent resected adenoma	913	Calcium carbonate 3 gm/d vs. placebo × 4 yrs	Adenoma recurrence adj. RR = 0.85 (95% CI = 0.74–0.98), p=0.03	Effective	Baron 1999
	Recent resected adenoma	1,429	Wheat bran fiber 13.5 gm/d vs. 2 gm/d × 5 yrs	Adenoma recurrence adj. OR = 0.88 (95% CI = 0.70–1.11), p = 0.28	Null	Alberts 2000
	Recent resected adenoma	2,079	Intensive low fat, high fiber, high fruits and vegetable diet vs. no intervention × 4 yrs	Adenoma recurrence RR = 1.00 (95% CI = 0.90–1.12)	Null	Schatzkin 2000
	Recent resected adenoma	665	Calcium gluconolactate/carbonate 2 gm/d vs. ispaghula husk 3.5 gm/d vs. placebo × 3 yrs	Adenoma recurrence: - calcium OR = 0.66 (95% CI = 0.38–1.17), p=0.16; - fiber OR = 1.67* (95% CI = 1.01–2.76), p=0.042	Null (Calcium) Deleterious (Fiber)	Bonithon-Kopp 2000
	Postmenopausal women	36,282	500 mg of elemental calcium as calcium carbonate with 200 IU of vitamin D3 bid vs. placebo × 7 yrs	CRC incidence: no significant difference between intervention & placebo groups HR, 1.08 (95% CI = 0.86–1.34); P=0.51	Null	Wactawski-Wende 2006
	Men aged 50 (African-American) or 55 (Caucasian) with serum PSA level 4 ng/mL and a DRE "not suspicious for prostate cancer"	35,533	Oral selenium (200 microg/d from L-selenomethionine) and matched vitamin E placebo, vitamin E (400 IU/d of all rac-alpha-tocopheryl acetate) and matched selenium placebo, selenium + vitamin E, or placebo + placebo × 7–12 yrs	CRC incidence: no significant difference between intervention & placebo groups Vitamin E: HR, 1.09 (0.69–1.73) Selenium: HR, 1.05 (0.66–1.67) Selenium + Vitamin E: HR, 1.28 (0.82–2.00) CRC mortality: No significant difference between intervention & placebo groups Vitamin E: HR, 1.30 (0.44–3.83) Selenium: HR, 1.00 (0.32–3.16)	Null	Lippman 2009

Organ System	Cohort	Sample Size	Intervention × Duration	Primary Efficacy Measure(s)	Effect of Intervention on Risk	Author & Year of Publication(s)
	FAP patients, 18 yo, who had previously undergone colectomy with ileorectal anastomosis	58	Enteric-coated formulation of EPA, as the free fatty acid EPA-FFA, 2g/d vs. placebo × 6 mos	Selenium + Vitamin E: HR, 1.49 (0.52–4.28) Polyp Number: 22.4% reduction in EPA group, P=0.012 Polyp Size: 29.8% reduction in sum of polyp diameters in EPA group, P=0.027	Effective	West 2010
	Recent resected adenoma	2259	Vitamin D3 1000IU/d, calcium 1200mg/d, both or neither × 3–5 yrs	RR for adenoma recurrence: Vitamin D3 alone: 0.97 (95% CI: 0.88–1.08) Calcium alone: 0.95 (95% CI: 0.85–1.06) Vitamin D3 + Calcium vs. Calcium alone: 0.99 (95% CI: 0.86–1.13)	Null	Baron 2014 (Presented at AACR Annual Meeting, Abstract CT335)
<b>Bladder</b>	Superficial bladder cancer	37	120 mg intravesical & 5 mg percutaneous BCG once a week × 6 wks following TUR vs. TUR alone	Tumor recurrence rate: 22% in TUR + BCG group vs. 42% in TUR alone (P=0.029)	Effective	Lamm 1980
	Recurrent superficial carcinoma of the bladder	88	120 mg intravesical & 5 mg percutaneous BCG once a week × 6 wks following TUR vs. TUR alone	No. of patients showing reduction in no. of recurrent tumors: 43 in TUR + BCG vs. 27 in TUR alone (P=0.001)	Effective	Pinsky 1985
	Recurrent superficial transitional cell carcinomas of the bladder	86	120 mg intravesical & 5 mg percutaneous BCG once a week × 6 wks following TUR vs. TUR alone	% with Disease Progression: 53% in TUR + BCG vs. 95% in TUR alone 10-yr Progression-Free Rate: 61.9% in TUR + BCG vs. 37% in TUR alone Survival Rate: 75% in TUR + BCG vs. 55% in TUR alone (P=0.03)	Effective	Herr 1988 Herr 1995
	Superficial transitional cell carcinoma	660	Intravesical & percutaneous BCG – induction and maintenance × 3 yrs vs. induction alone	Median recurrence-free survival = 35.7 vs. 76.8 mos, p<0.0001	Effective	Lamm 2000
	BCG-refractory CIS of the bladder	90	800 mg intravesical valrubicin once a week × 6 wks (open label, non-comparative, pivotal phase III study)	Per cent complete responders (disease-free at 3 & 6 mo F/U): 21%	Effective	Steinberg 2000

Organ System	Cohort	Sample Size	Intervention × Duration	Primary Efficacy Measure(s)	Effect of Intervention on Risk	Author & Year of Publication(s)
Skin	Recurrent CIS after failed multiple courses of intravesical therapy, including at least 1 course of BCG ("Pivotal Phase III") CIS alone or with papillary disease (Ia/T1) and failed BCG, were BCG intolerant or BCG was contraindicated ("A9303")	90 80	800 mg of valrubicin once a week × 6 wks (open label, non-comparative study) 800 mg of valrubicin once a week × 6 – 9 wks	Pivotal phase III – Per cent complete responders (disease free at primary disease evaluation & 3 mo F/U): 18% A9303 Phase II/III study – Per cent complete responders: 18%	Effective	Dinney 2013
	Resected nonmelanoma skin cancer	1,805	B-carotene 50 mg/d vs. placebo × 5 yrs	Secondary non-melanoma skin cancers: RR = 1.05 (95% CI = 0.91–1.22)	Null	Greenberg 1990
	Resected basal cell cancer	981	Isotretinoin 10 mg/d vs. placebo × 3 yrs	Percentage of patients with incident basal cell cancers – no significant difference; Annual rate of incident basal cell cancers – no significant difference	Null	Tangrea 1992
	Resected basal or squamous cell cancer	525	Retinol 25,000 IU/d vs. isotretinoin 5–10 mg/d vs. placebo × 3 yrs	Time to first skin cancer – no significant difference; Number of incident skin cancers – no significant difference	Null	Levine 1997
	Resected basal cell or squamous cell cancer	1,312	Selenium 200 mcg/d vs. placebo × mean 4.5 yrs	Basal cell cancer incidence RR = 1.10 (95% CI = 0.95–1.28); Squamous cell cancer incidence RR = 1.14 (0.93–1.39); Secondary analyses: - Colon cancer incidence RR = 0.42 (95% CI = 0.18–0.95); - Lung cancer incidence RR = 0.54* (95% CI = 0.30–0.98); - Prostate cancer incidence RR = 0.37, p = 0.002 - Total cancer incidence RR = 0.63 (95% CI = 0.47–0.85) - All-cause mortality RR = 0.50 (95% CI = 0.31–0.80)	Null (Effective in secondary analyses for incidence of other cancers, total incidence and all-cause mortality)	Clark 1996, 1998
	Resected actinic keratoses and/or skin cancers	2,297	Retinol 25,000 IU/d vs. placebo × 5 yrs	Squamous cell cancer incidence – reduced in those with prior AK's, p = 0.04; otherwise no significant effects	Effective (borderline; in those with prior AKs)	Moon 1997
	Healthy male physicians aged 40–84 years	22,071	BC 50 mg QOD vs. placebo × 12 yrs	Nonmelanoma skin cancer incidence RR = 0.98 (95% CI = 0.92–1.05);	Null	Frieling 2000

Organ System	Cohort	Sample Size	Intervention × Duration	Primary Efficacy Measure(s)	Effect of Intervention on Risk	Author & Year of Publication(s)
	Xeroderma pigmentosum patients	30	Topical T4N5 liposome lotion vs. placebo × 12 mos	Basal cell cancer incidence RR = 0.99 (95% CI = 0.92–1.06); Squamous cell cancer incidence RR = 0.97 (95% CI = 0.84–1.13)	Effective	Yarosh 2001
	Prevalent actinic keratoses	36	Topical 20% aminolevulinic acid hydrochloride with fluorescent blue light vs. vehicle × 1 single treatment	Annual rate of new actinic keratoses: Rx = 8.2 vs. placebo = 25.9, * yielding a difference of 17.7 (95% CI = 11.8–26.5); Annual rate of basal cell cancers: Rx = 3.8 vs. placebo = 5.4, yielding a difference of 1.6 (95% CI = 0.38–2.82)	Effective	Jeffes 2001
	Prevalent actinic keratoses	Not specified	Topical 3% diclofenac in 2.5% hyaluronic acid gel BID vs. vehicle × up to 90 days	Actinic keratosis regression: Treated vs. control = 33% at 60 days, 50% at 90 days *	Effective	Jarvis 2003
	Renal allograft recipients with more than 10 prevalent AK's	44	Acitretin 30 mg/d vs. placebo × 6 mos	Squamous cell cancer incidence: Treated vs. control = 11% vs 47%, p = 0.01; Actinic keratosis incidence: Treated vs. control = 13.4 vs. 28.2 (41.6% reduction; 95% CI: 11.5–71.7)	Effective	Bavinck 1995
	Healthy adults with 4–8 actinic keratoses on face or balding scalp (not both)	436	Imiquimod 5% cream vs. placebo once daily for 2 d/wk × 16 wks	Complete clearance rate (proportion at the 8-week post-treatment visit with a count of 0 clinically visible AK lesions): 45.1% vs. 3.2% (P < 0.001)	Effective	Lebwohl 2004
	Adults with 5–20 actinic keratoses	490	Imiquimod 2.5% or 3.75% cream vs. placebo once daily × two 3-wk treatment cycles separated by a 3-wk no-treatment cycle	Complete clearance rate: 25% (2.5% cream) vs. 34% (3.75% cream) vs. 5.5% (placebo) P < .001	Effective	Hanke 2010
	Adults with 5–20 actinic keratoses	479	Imiquimod 2.5% or 3.75% cream vs. placebo once daily × two 2-wk	Complete clearance rate:	Effective	Swanson 2010



Organ System	Cohort	Sample Size	Intervention × Duration	Primary Efficacy Measure(s)	Effect of Intervention on Risk	Author & Year of Publication(s)
			treatment cycles separated by a 2-wk no-treatment cycle	30.6% (2.5% cream) vs. 35.6% (3.75% cream) vs. 6.3% (placebo) <i>P</i> < 0.001		
	10–40 actinic keratoses	240	Celecoxib 200 mg BID vs. placebo × 9 mos	Actinic keratosis incidence: no difference between the two groups at 9 months after randomization Non-melanoma skin cancers: (RR = 0.41, 95% CI = 0.23 to 0.72, <i>P</i> = .002); BCC (RR = 0.40, 95% CI = 0.18 to 0.93, <i>P</i> = .032); SCC (RR = 0.42, 95% CI = 0.19 to 0.93, <i>P</i> = .032)	Null (Effective in secondary analyses for non-melanoma skin cancers)	Elmets 2010
	Prior history of skin cancer (mean 4.5 NMSC)	291	DFMO 500 mg/m <sup>2</sup> /day vs. placebo × 4–5 yrs	Control vs. DFMO NMSC (0.60 vs. 0.44 per person per year; <i>p</i> =0.062) BCC (0.40 vs. 0.28 per person per year; <i>p</i> =0.03) cuSCC (0.19 vs. 0.15 per person per year; <i>p</i> =0.565)	Null (Effective in secondary analyses for BCC)	Bailey 2010
	U.S. veterans (96% male), history of >=2 BCC or cSCC on face within 5 years	1,131	Topical tretinoin 0.1% cream vs. vehicle × 1.5 – 5.5 yrs	Tretinoin vs. Control BCC at 5 years 53% vs. 54%, <i>P</i> =0.3 cuSCC at 5 years 28% vs. 31%, <i>P</i> =0.4 No difference in AK counts	Null	Weinstock 2012
	Nontransplant adults with history of >=2 NMSC within 5 years	70	Acitretin 25 mg PO QD 5d/week vs. placebo × 2 years	Acitretin vs. Control NMSC incidence: 54% vs. 74%, OR= 0.41 (95% CI: 0.15–1.13) <i>P</i> =0.13	Null	Kadakia 2012
	Patients 18 y.o. with actinic keratoses	547 (Face or scalp studies) 458 (Trunk or extremities studies)	Ingelol mebutate 0.015% vs. placebo self-applied once daily × 3 consecutive days Ingelol mebutate 0.05% vs. placebo self-applied once daily × 2 consecutive days (trunk or extremities)	Complete clearance of all clinically visible actinic keratoses in target treatment area on day 57: 42.2% vs. 3.7% ( <i>P</i> <0.001) 34.1% vs. 4.7% ( <i>P</i> <0.001)	Effective	Lebwohl 2012
	Basal cell nevus syndrome patients	42	Vismodegib 150 mg daily vs. placebo × 18 mos	Comparative rate of appearance of new basal-cell carcinomas that were surgically eligible: 2 vs. 29 BCCs per patient per year, <i>p</i> <0.001	Effective	Tang 2012

Organ System	Cohort	Sample Size	Intervention × Duration	Primary Efficacy Measure(s)	Effect of Intervention on Risk	Author & Year of Publication(s)
Oral/Head & Neck	Oral leukoplakia	44	Isotretinoin 1–2 mg/kg/d vs. placebo × 3 mos	Leukoplakia regression (major reduction size) in 85%*, p=0.0002; reversed dysplasia in 81%, p=0.01	Effective	Hong 1986
	Resected HNSCC	103	Isotretinoin 50–100 mg/m <sup>2</sup> /d vs. placebo × 12 mos	Second primary tumors – reduced 83%, p=0.005	Effective	Hong 1990
	Oral leukoplakia (mucosal hyper- or dysplasia)	70 (59) <sup>c</sup>	Isotretinoin 1.5 mg/kg/d × 3 mos; responders randomized to isotretinoin 0.5 mg/kg/d vs. β-carotene 30 mg/d × 9 mos	Leukoplakia regression: Isotretinoin vs. β-carotene – 92% vs. 45% response, p<0.001	Effective	Lippman 1993
	Stage I/II HNSCC definitively treated with XRT or surgery	1,190	Isotretinoin (30 mg/d) vs. placebo × 3 yrs & followed for 4 additional yrs	Second primary tumors – not significantly reduced; - HR = 1.06, 95% CI = 0.83 – 1.35 Survival – not significantly increased; - HR = 1.03, 95% CI = 0.81 to 1.32	Null	Khuri 2006
	Resected HNSCC	316	Etretinate 25–50 mg/d vs. placebo × 24 mos	Second primary tumors – not significantly reduced	Null	Bolla 1994
	Resected HNSCC or lung cancer	2,592	Retinyl palmitate 150–300 IU/d vs. N-acetylcysteine 600 mg/d vs. both vs. neither × 2 yrs	Second primary tumors – not significantly reduced; Overall survival or event-free survival not significantly reduced	Null	van Zandwijk 2000
Lung	Patients with OPLs (Non-inferiority trial)	162	13cRA (0.5 mg/kg/d orally for 1 year followed by 0.25 mg/kg/d orally for 2 years) or BC (50 mg/d orally) plus RP (25,000 U/d orally) for 3 years and later (by protocol revision) to 13cRA or RP alone × 3 yrs & followed for 2 additional yrs	OPL clinical response rate at 3 months – not statistically equivalent - combined BC plus RP and RP alone arm (32.5%) was not statistically equivalent to that of 13cRA (48.1%). Oral cancer-free survival – not significantly different - 5-year oral cancer-free survival rates of the three arms: 78% (13cRA), 84% (BC plus RP), and 82% (RP); P = .66 for the overall comparison)	Equivalence of RP plus BC or RP alone with low-dose 13cRA not established	Papadimitrakopoulou, 2009
	Male smokers 50–69 years old	29,133	AT 50mg/d vs. BC 20mg/d vs. both vs. neither × 5–8 yrs AT 50 mg/d vs. BC 20 mg/d vs. both vs. neither	Primary lung cancer incidence AT = 2% reduction (95% CI = -14% to +12%); BC = 18% increase (95% CI = 3–36%)	Deleterious	ATBC 1994 Virtamo 2003

Organ System	Cohort	Sample Size	Intervention × Duration	Primary Efficacy Measure(s)	Effect of Intervention on Risk	Author & Year of Publication(s)
			× 5-8 yrs with 6-8 yrs of additional follow-up	<p>Secondary analyses –                      Prostate cancer incidence                      AT = 32% * reduction                      BC = 23% (NS) increase                      Cancer mortality                      AT = 41% * reduction                      BC = 15% (NS) increase                      With 6-8 yrs of additional follow-up                      No significant effects on any cancer;                      Overall mortality                      AT RR = 1.01 (95% CI = 0.96–1.05)                      BC RR = 1.07 (95% CI = 1.02–1.12)</p>		
	Smokers, former smokers, and workers exposed to asbestos	18,314	BC 30 mg/d + retinol 25,000 IU/d vs. placebo × 5 yrs	<p>Primary lung cancer incidence                      RR = 1.28 (95% CI = 1.04–1.57), p = 0.02; Lung cancer mortality RR = 1.46 (95% CI = 1.07–2.00)</p>	Deleterious	Omnenn 1996
	Male physicians 40-84 years old	22,071	BC 50 mg QOD vs. ASA 325 mg QOD vs. both vs. placebo × 12 yrs	<p>ASA terminated early                      Beta carotene results:                      Cancer incidence RR=0.98, (95% CI=0.91–1.06)                      Secondary analyses-                      Lung cancer Incidence                      Current smoker RR=0.90 (95% CI=0.58–1.40)                      Former smoker RR=1.00 (95% CI=0.62–1.61)                      Never smoker RR=0.78 (95% CI=0.34–1.79)                      Cancer mortality RR=1.02 (95% CI=0.89–1.18)</p>	Null	Hennekens 1996
	Resected NSCLC or head & neck cancer	2,592	RP 300,000IU/d × 1 yr, then 150,000 IU/d × 1 yr vs. NAC 600 mg/d × 2 yrs vs. both vs. no intervention	<p>5-yr overall survival                      71% vs. 72% (NAC vs. no NAC)                      70% vs. 73% (RP vs. no RP)                      No effect on event-free survival or second primary tumor</p>	Null	Van Zandwijk 2000
	Resected stage I non-small cell lung cancer	1,166	Isotretinoin 30 mg/d vs. placebo × 3 yrs	<p>Second primary tumor HR = 1.08 (95% CI = 0.78–1.49);                      Tumor recurrence HR = 0.99 (95% CI = 0.76–1.29);                      Mortality HR = 1.07 (95% CI = 0.84–1.35)</p>	Null	Lippman 2001

Organ System	Cohort	Sample Size	Intervention × Duration	Primary Efficacy Measure(s)	Effect of Intervention on Risk	Author & Year of Publication(s)
	Resected stage I non-small cell lung cancer 18 years	1,772	Selenium 200 µg/d vs. placebo × 48 mos (selenized yeast)	Second primary tumor Lung ca. SPT: 1.62 vs. 1.30 per 100 person-yrs (Se vs. plac) Overall SPT: 3.54 vs. 3.39 per 100 person-yrs (Se vs. plac) P=.294 5-yr DFS: 74.4% vs. 79.6% (Se vs. plac) P=.069 5-yr OS: 76.8% vs. 79.9% (P=.154)	Null	Karp 2013
<b>Prostate</b>	Men >50 years of age	18,882	Finasteride 5 mg/d vs. placebo × 7 yrs	Seven-year period prevalence = 24.8% * reduction (95% CI = 18.6–30.6), p<0.001; Gleason grade 7–10 more common * in the treated group. p<0.001	Effective (but increased high-grade tumors)	Thompson 2003
	Men aged 50 (African-American) or 55 (Caucasian) with serum PSA level 4 ng/mL and a DRE "not suspicious for prostate cancer (SELECT)	35,533	Oral selenium (200 µg/d from L-selenomethionine) with matched vitamin E placebo Vitamin E (400 IU/d of all rac -α-tocopheryl acetate) with matched selenium placebo Both agents, or Both matched placebos x a minimum of 7 yrs and maximum of 12 yrs	Hazard ratios for prostate cancer in 2008 were: - 1.13 (99% CI = 0.95–1.35; n = 473) for vitamin E - 1.04 (99% CI = 0.87–1.24; n = 432) for selenium - 1.05 (99% CI = 0.88–1.25; n = 437) for selenium + vitamin E vs. 1.00 (n = 416) for placebo. Hazard ratios for prostate cancer in 2011 were: - 1.17 (99% CI = 1.004–1.36) for vitamin E - 1.09 (99% CI = 0.93–1.27) for selenium - 1.05 (99% CI = 0.89–1.22) for selenium + vitamin E	Null	Lippman 2009 Klein 2011
	Men ages 50 to 75 with a PSA of 2.5 to 10.0 ng per milliliter, and 1 negative prostate biopsy within 6 months before enrollment	8,231	Dutasteride 0.5 mg/d × 4 yrs	Incident prostate cancer RR = 23% reduction (95% CI = 15.2–29.8); P < 0.001 (AR) 5% decrease (AR high grade) 0.5% increase	Effective (but increased high-grade tumors)	Andriole, 2010
<b>Stomach (Gastric, N</b>	Participants of Linxian, China 40–69 years old at high risk for gastroesophageal cancers	29,584	Complex factorial design with 4 arms: - retinol + zinc - riboflavin + niacin - vitamin C + molybdenum - BC + vitamin E + selenium × 1–5 yrs	Stomach cancer incidence RR = 0.79 (95% CI = 0.64–0.99) with BC + vitamin E + selenium 15-yr follow-up Stomach cancer mortality HR = 0.89 (95% CI = 0.79–1.00), P = 0.043 with BC + vitamin E + selenium	Effective (borderline: BC + vitamin E + selenium)	Blot 1993 Qiao 2009

Organ System	Cohort	Sample Size	Intervention × Duration	Primary Efficacy Measure(s)	Effect of Intervention on Risk	Author & Year of Publication(s)
	Residents of Narino, Columbia with precancerous lesions	852	Anti- <i>Helicobacter</i> antibiotics +/- $\beta$ -carotene +/- ascorbic acid vs. placebo × 6 yrs	Stomach cancer mortality HR(< 55) = 0.83 (95% CI = 0.69–1.00) P = 0.046 with BC + vitamin E + selenium Stomach cancer mortality HR( 55) = 0.93 (95% CI = 0.80–1.07) P = 0.307 with BC + vitamin E + selenium	Effective	Correa 2000
	Healthy carriers of <i>H. pylori</i> in Fujian Province, China	1630	<i>H. pylori</i> eradication treatment (2 week course of omeprazole 20mg, combo of amoxicillin & clavulanate potassium 750mg, and metronidazole 400mg, all twice daily) vs placebo	GC incidence: no statistically significant difference between treatment vs placebo after 7.5 yrs of follow-up Sub-group analysis in <i>H. pylori</i> carriers without precancerous lesions: GC incidence: P=0.02 (by Kaplan-Meier analysis)	Null (Effective in subgroup analysis of those without precancerous lesions)	Wong 2004
	Adults 35–64 yo. from Shandong Province, China	3365	Factorial design: amoxicillin & omeprazole for 2 weeks; vitamin C, vitamin E, & selenium for 7.3 yrs. (vitamin supplement); aged garlic extract & steam-distilled garlic oil for 7.3 yrs (garlic supplement)	OR for combined endpoint of dysplasia or gastric cancer: - 1.13 (0.89–1.44), P=0.32 for <i>H. pylori</i> treatment - 1.10 (0.89–1.37), P=0.39 for vitamin supplement - 0.98 (0.79–1.22), P=0.86 for garlic supplement OR for second combined endpoint of severe chronic atrophic gastritis, intestinal metaplasia, dysplasia, or gastric cancer - 0.77 (0.62–0.95), P=0.016 for <i>H. pylori</i> treatment - 1.32 (1.12–1.57), P=0.001 for vitamin supplement - 0.99 (0.84–1.18), P=0.94 for garlic supplement <i>15-year effects</i> Gastric cancer incidence ORs: for <i>H. pylori</i> treatment - 0.61 (0.38–0.96), P=0.032 for <i>H. pylori</i> treatment + vitamin supplement - 0.81 (0.54–1.22), P=0.32 for vitamin supplement - 0.80 (0.53–1.20), P=0.28 for garlic supplement	H. pylori – Effective (2 <sup>nd</sup> combined endpoint and gastric cancer incidence at 15-yr follow-up) Vitamin supplement – Effective (2 <sup>nd</sup> combined endpoint only) Garlic supplement – Null	You 2006 Ma 2012

Organ System	Cohort	Sample Size	Intervention × Duration	Primary Efficacy Measure(s)	Effect of Intervention on Risk	Author & Year of Publication(s)
	Adults 35–64 y.o. from Shandong Province, China with <i>H. pylori</i> infection and advanced gastric lesions	1024	Factorial design: anti- <i>H. pylori</i> treatment (omeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg, BID) for 7 days and celecoxib (200mg BID) for 24 mos	Gastric cancer mortality HRs: - 0.67(0.36–1.28), P=0.22 for <i>H. pylori</i> treatment - 0.55 (0.29–1.03), P=0.06 for vitamin supplement - 0.65 (0.35–1.20), P=0.17 for garlic supplement	Celecoxib – Effective <i>H. pylori</i> – Effective <i>H. pylori</i> followed by Celecoxib – Null	Wong 2012
<b>Liver</b>	Chronic active hepatitis C with cirrhosis	90	Interferon-α 6 MU TIW vs. symptomatic Rx × 12–24 wks with 2–7 yrs follow-up	ORs for regression of lesions: 1.72 (95% CI = 1.07–2.76), P=0.026 for celecoxib alone 2.19 (95% CI = 1.32–3.65), P=0.002 for <i>H. pylori</i> treatment alone 1.48 (95% CI = 0.91–2.40), P=0.117 for <i>H. pylori</i> treatment followed by celecoxib	Effective	Nishiguchi 1995
	Prior resected or alcohol-ablated liver cancer	89	Polyrenoic acid 600 mg/d vs. placebo × 12 mos	Second primary cancer incidence RR = 0.31 * (95% CI = 0.12–0.78)	Effective	Muto 1996
	Male patients with chronic hepatitis B infection	101	Interferon vs. interferon with prednisolone priming vs. placebo × 12 wks	Cumulative primary cancer incidence – 87% * reduction, p=0.013	Effective	Lin 1999
	Compensated hepatitis C-related cirrhosis	99	Interferon α-2b 3 MU TIW vs. no treatment × 48 wks	Primary cancer incidence – no significant effect	Null	Valla 1999
	Chronic hepatitis B with cirrhosis or advanced fibrosis	651	Lamivudine (100 mg/d) vs. placebo × 5 yrs	HCC incidence: HR = 0.49 (95% CI = 0.25–0.99), P=0.047	Effective (borderline)	Liaw 2004
<b>Overall cancer incidence and mortality</b>	Residents of Linxian, China 40–69 years old at high risk for gastroesophageal cancers	29,584	Complex factorial design with 4 arms: - retinol + zinc - riboflavin + niacin - vitamin C + molybdenum - BC + vitamin E + selenium × 1–5 yrs	Overall cancer incidence RR = 0.87 (95% CI = 0.75–1.00) with BC + vitamin E + selenium Overall mortality RR = 0.91 (95% CI = 0.84–0.99) with BC + vitamin E + selenium 15-yr. follow-up Overall mortality HR = 0.95 (95% CI = 0.91–0.99) P = 0.009 with BC + vitamin E + selenium Overall mortality HR (<55) = 0.88 (95% CI = 0.82–0.95),	Effective (Overall mortality, esp. at 15-yr follow-up; and cancer mortality at 15-yr follow-up in subgroup analysis)	Blot 1993 Qiao 2009

Organ System	Cohort	Sample Size	Intervention × Duration	Primary Efficacy Measure(s)	Effect of Intervention on Risk	Author & Year of Publication(s)	
				<p><math>P &lt; 0.001</math> with BC + vitamin E + selenium                      Overall mortality HR ( 55) = 0.98 (95% CI = 0.93–1.03), <math>P = 0.367</math> with BC + vitamin E + selenium                      Overall cancer mortality HR = 0.95 (95% CI = 0.89–1.02), <math>P = 0.148</math> with BC + vitamin E + selenium                      Overall cancer mortality HR (&lt; 55) = 0.85 (95% CI = 0.76–0.95), <math>P = 0.003</math> with BC + vitamin E + selenium                      Overall cancer mortality HR (&lt; 55) = 1.02 (95% CI = 0.94–1.12), <math>P = 0.976</math> with BC + vitamin E + selenium</p>			
	Healthy male physicians 40–84 years old	22,071	BC 50 mg QOD vs. placebo × 12 yrs	<p>Overall cancer incidence RR = 0.98 (95% CI = 0.91–1.06);                      Cancer mortality RR = 1.02 (95% CI = 0.89–1.18)</p>	Null	Hennekens 1996	
	Physicians' Health Study II (males aged 50 yrs)	14,641	Multivitamin (Centrum Silver) vs. placebo × 11.2 yrs (median treatment & follow-up)	<p>Overall cancer incidence: HR = 0.92 (95% CI: 0.86–0.998), <math>P = .04</math>                      Cancer mortality: HR = 0.88 (95% CI: 0.77–1.01), <math>P = 0.07</math>                      Overall mortality: HR = 0.94 (95% CI: 0.88–1.02), <math>P = 0.13</math>                      No significant cancer site-specific findings.</p>	Null (Borderline effective for overall cancer incidence)	Gaziano 2012	

AT=alpha-tocopherol; BC=beta-carotene; RP=retinyl palmitate; OPLs = Oral Premalignant Lesions; NAC= N-Acetylcysteine; SPT= Second primary tumor; DFS = disease-free survival; OS= overall survival; CIN = cervical intraepithelial neoplasia; NMSC = non-melanoma skin cancer; AR = absolute risk; HR = Hazard Ratio; Wks=weeks; Mos=months; Yrs=years; # Phase IIb trial, but no Phase III trials conducted for esophageal adenocarcinoma (EAC; AsPECT trial is on-going and is expected to report results on EAC);

\* Statistically significant