ARTICLE TITLE: Molecular Cancer Prevention: Current Status and Future Directions

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1. Discuss benefits and limitations of a range of agents for treatment of precancerous lesions or cancer risk reduction
2. Identify and manage patients who may benefit from these agents in clinical practice

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Molecular Cancer Prevention: Current Status and Future Directions

Karen Colbert Maresso, MPH; Kenneth Y. Tsai, MD, PhD; Powel H. Brown, MD, PhD; Eva Szabo, MD; Scott Lippman, MD; Ernest T. Hawk, MD, MPH

The heterogeneity and complexity of advanced cancers strongly support 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 (eg, aspirin) in common chronic diseases, including cancer; and a successful track record of more than 10 agents approved by the US Food and Drug Administration 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 it 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, several challenges to the field must be addressed. Here, the authors provide a brief overview of the context for and special considerations of molecular prevention along with a discussion of the results from major randomized controlled trials. CA Cancer J Clin 2015;65:345-383. © 2015 American Cancer Society.

Keywords: molecular prevention, chemoprevention, prevention, randomized controlled trial

Introduction
Premise and Context for Molecular Prevention

Recent data from sequencing cancer genomes highlight the extent of genetic complexity characteristic of invasive, metastatic (advanced) cancers. 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 comprehensive therapy.

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Chemoprevention is one form of molecular prevention that targets events occurring, before invasion across the basement membrane. The heterogeneity and complexity of advanced cancers strongly support 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. Cancer prevention occurs across the entire disease spectrum, from primary to tertiary prevention, and encompasses several 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, before invasion across the basement membrane. Chemoprevention is one form of molecular prevention that was defined by Dr. Michael Sporn and colleagues in 1976. 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 because of microbial or other diseases (eg, 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 toward cancer prevention. We now have refined insights into cancer etiology and early pathogenesis; successful risk models; the promise of agents with broad preventive efficacy (eg, aspirin) in common chronic diseases, including cancer; and a successful track record of more than 10 agents approved by the US Food and Drug Administration (FDA) for the treatment of precancerous lesions or cancer risk reduction (Table 1). In addition to these agents, there are also several interventions targeted to viruses and bacteria associated with various cancers (Table 2) that, although 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 from major randomized controlled trials (RCTs) of molecular preventive agents by cancer site. Table 3 provides a compendium of phase 3 (and some phase 2) clinical trials by cancer site.

**Considerations of Molecular Prevention as a Strategy**

The premise of molecular strategies to prevent cancer is supported by several lines of evidence. First, decades of research have revealed many of the mechanisms of carcinogenesis and have demonstrated that it is a multistep 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 that these agents are both effective and safe in significantly reducing the risk of cancer, offering definitive proof of principle of the concept of molecular prevention in cancer 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. Finally, and most recently, sequencing of cancer genomes has revealed the extensive genetic heterogeneity and profound genomic instability of advanced neoplasms, 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. 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. 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 the treatment of invasive disease in isolation.

The development of molecular preventive agents does not differ significantly from the development of therapies for advanced cancers, yet it has unique challenges and special considerations. 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-level 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). Although 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. Because of 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 are available.140 Because 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 al141), 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 (ie, 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 non-steroidal anti-inflammatory drugs (NSAIDs) to prevent familial forms of colorectal cancer (CRC).47,51,142 Therefore, the 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. RCTs 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, because 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 are necessary to achieve regulatory approval and to promote acceptance in the marketplace. Sponsorship of a trial can also affect the overall design, because private investment, while often yielding more resources, can also lead to nontrivial 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 biologic, efficacy markers. Indeed, only two of the FDA-approved preventive agents are for use in relatively inaccessible organs (eg, tamoxifen and raloxifene in breast cancer), whereas 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 that often occurs 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.
| AGENT                           | TARGETED COHORT IN INDICATION*                                                                 | FDA INDICATION*                                                                 |
|--------------------------------|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Tamoxifen                      | Women with DCIS after 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 age 35 y with a 5-y predicted risk of breast cancer ≥ 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 [CIS] or atypical hyperplasia, one or more first-degree relatives with breast cancer, or a 5-y predicted risk of breast cancer ≥ 1.66% (based on the modified Gail model)) | Reduction in risk of invasive breast cancer                                      |
| Human papillomavirus (HPV) vaccine (Cervarix) | Females ages 9-25 y | Prevention of the following diseases caused by oncogenic HPV types 16 and 18:  
  - Cervical cancer  
  - Cervical intraepithelial neoplasia (CIN) grade II or worse and adenocarcinoma in situ  
  - CIN grade I |
| HPV vaccine (Gardasil 9)       | Girls and women ages 9-26 y | Prevention of the following diseases caused by HPV types included in the vaccine:  
  - Cervical, vulvar, vaginal, and anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58  
  - Genital warts caused by HPV types 6 and 11  
  And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:  
  - CIN grade II/III and cervical adenocarcinoma in situ  
  - CIN grade I  
  - Vulvar intraepithelial neoplasia grade 2 and grade 3  
  - Vaginal intraepithelial neoplasia grades 2 and grade 3  
  - Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3 |
| HPV vaccine (Gardasil 9)       | Boys and men ages 9-15 y | Prevention of the following diseases caused by HPV types included in the vaccine:  
  - Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58  
  - Genital warts caused by HPV types 6 and 11  
  And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:  
  - AIN grades 1, 2, and 3 |
| Photodynamic therapy (PDT) with Photofrin | Males and females with high-grade dysplasia in Barrett esophagus (BE) | Ablation of high-grade dysplasia in patients with BE who do not undergo esophagectomy |
| Celecoxib                      | Males and females aged ≥ 18 y with familial adenomatous polyposis (FAP)                        | Reduction in the no. of adenomatous colorectal polyps in FAP, as an adjunct to usual care (eg, endoscopic surveillance, surgery) |
| Bacillus Calmette-Guerin (BCG) | Males and females with CIS of the urinary bladder                                             | Intravesical use in the treatment and prophylaxis of CIS of the urinary bladder and for the prophylaxis of primary or recurrent stage Ta and/or T1 papillary tumors after transurethral resection |
| Valrubicin                     | Males and females with BCG-refractory CIS                                                      | Intravesical therapy of BCG-refractory 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                         |
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) breast cancers, which are negative for ER, progesterone receptor (PR), and HER2. Because of the disparity in efficacy of prevention agents for each of these distinct tumor types, below, we discuss the major chemoprevention approaches currently in clinical use, or with high potential in the near future, individually by each specific subtype.

Phase 3 trials are listed in Table 3.

ER-positive breast cancer: Selective ER modulators.

Selective ER modulators (SERMs) represent the first successful agents for the prevention of breast cancer. Because these are ER modulators, by definition, SERMs are most effective for patients at high risk of ER-positive breast cancer. After positive results from clinical treatment trials investigating tamoxifen in women with early stage breast cancer, several phase 3 breast cancer prevention trials were conducted studying the effectiveness of tamoxifen for women at high risk of breast cancer. The results of those studies demonstrated that tamoxifen reduces invasive ER-positive breast cancer by 30% to 60%, and led to FDA approval for the use of tamoxifen in high-risk women for breast cancer risk reduction (Table 1). Although 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, or stroke) and increased risk of uterine cancer. Data from trials of tamoxifen in the adjuvant setting suggest a dose-dependent and duration-dependent risk of side effects. Consequently, work is ongoing in the preventive setting to optimize the tamoxifen regimen through dose reduction, combinations with other agents, intermittent dosing, and/or topical administration.

Treatment with the second-generation SERM raloxifene reportedly produced preventive effects similar to those of tamoxifen (a 45%-90% decrease in invasive ER-positive tumors) and with reduced side effects, including no increase in the risk of uterine cancer. Those studies resulted in the FDA approval of raloxifene as an alternative to tamoxifen for breast cancer risk reduction in high-risk women (Table 1). However, treatment with raloxifene is still associated with an increased risk of hot flushes and

### TABLE 1. Continued

| AGENT | TARGETED COHORT IN INDICATION | FDA INDICATION |
|-------|-------------------------------|---------------|
| Diclofenac sodium | Males and females with actinic keratoses | Topical treatment of actinic keratoses |
| 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 |
| Masoprocolc | 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 |

*This information is according to the US Food and Drug Administration product label. *US Food and Drug Administration labeling was voluntarily withdrawn by Pfizer in 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

| INFECTIOUS ORGANISM | ASSOCIATED CANCER | INTERVENTION (REFERENCE) |
|---------------------|-------------------|--------------------------|
| Hepatitis B virus   | Hepatocellular carcinoma | Hepatitis B vaccine, interferon therapy, nucleoside analogues (Chou 2014) |
| Hepatitis C virus   | Hepatocellular carcinoma | Interferon therapy, nucleoside analogues (Chou 2013) |
| Human immunodeficiency virus | Kaposi sarcoma and non-Hodgkin lymphoma | Antiretroviral therapies (Ray 2010) |
| Helicobacter pylori | Gastric/stomach cancer | Antibiotics (Graham 2014), "triple/quadruple therapy" |
| Schistosomiasis     | Bladder cancer     | Antischistosomals (Kramer 2014), praziquantel and metrifonate |
| ORGAN SYSTEM                  | COHORT                                                                 | SAMPLE SIZE | INTERVENTION × DURATION | PRIMARY EFFICACY MEASURE(S)                                                                                                   | EFFECT OF INTERVENTION ON RISK | AUTHOR AND YEAR OF PUBLICATION(S) |
|------------------------------|------------------------------------------------------------------------|-------------|-------------------------|----------------------------------------------------------------------------------------------------------------------------------|-------------------------------|-----------------------------------|
| Breast                       | Women with resected stage I cancer or DCIS                            | 2972        | Fenretinide 200 mg/d vs placebo × 5 y | 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, 19998.9            |
|                              | Women with increased risk of breast cancer (Gail model; NSABP-P1/BCPT) | 13,388      | Tamoxifen 20 mg/d vs placebo × 5 y | Invasive breast cancer incidence: RR, 0.51 (P<0.0001); noninvasive breast cancer incidence: RR, 0.50 (P<0.02)                  |
|                              |                                                                        |             |                         | Effective                                                                                                                         |                               | Fisher 199810                     |
|                              | Women with family history of breast cancer (Royal Marsden)            | 2471        | Tamoxifen 20 mg/d vs placebo × median of 70 mo | Primary cancer incidence: RR, 1.06 (95% CI, 0.7-1.7; P = .8)                                                                         |
|                              |                                                                        |             |                         | Null                                                                                                                              |                               | Powles 199612                     |
|                              | Women with normal risk, posthysterectomy                              | 5408        | Tamoxifen 20 mg/d vs placebo × 5 y | 20-Y follow-up: Invasive breast cancer: HR, 0.78 (95% CI, 0.58-1.04; P = .1); ER+ breast cancer: HR, 0.61 (95% CI, 0.43-0.86; P = .005); secondary planned analysis |
|                              |                                                                        |             |                         | Effective for ER+ at 20-y follow-up                                                                                              |                               | Powles 200713                     |
|                              | Women with increased risk of breast cancer (>2-fold RR; IBIS-I)       | 7139        | Tamoxifen 20 mg/d vs placebo × 5 y | Primary cancer incidence: Risk reduction, 32% (95% CI, 8%-50%; P = .013)                                                          |
|                              |                                                                        |             |                         | Effective                                                                                                                         |                               | IBIS Investigators 200216         |
|                              | High-risk, postmenopausal women aged >35 y (NSABP-P2/STAR)           | 19,747      | Tamoxifen 20 mg/d or raloxifene 60 mg/d × 5 y | Invasive breast cancer: RR, 1.02 (95% CI, 0.82-1.28); noninvasive breast cancer: RR, 1.40 (95% CI, 0.98-2.00)               |
|                              |                                                                        |             |                         | Raloxifene as effective as tamoxifen                                                                                              |                               | Vogel 200618                      |
|                              | Postmenopausal women with low BMD, aged <80 y (MORE)                 | 7705        | Raloxifene 60 or 120 mg/d or placebo × 4 y | 3-Y results: Breast cancer incidence: RR, 0.24 (95% CI, 0.13-0.44; P<.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) |
|                              |                                                                        |             |                         | Effective (ER+ only)                                                                                                              |                               | Cummings 199910                   |
|                              | Postmenopausal women with low BMD reconceived from the MORE trial, aged <80 y (CORE) | 4011        | Raloxifene 60 mg/d or placebo × an additional 4 y after 4 y of raloxifene on MORE trial | Incidence of invasive breast cancer: HR, 0.41 (95% CI, 0.24-0.71); ER+ invasive breast cancer: HR, 0.34 (95% CI, 0.18-0.66); no difference between the 2 groups in incidence of ER− invasive breast cancer (P = .86); over 8 y of MORE + CORE: Incidence of invasive breast cancer: HR, 0.34 (95% CI, 0.22-0.50); ER+ invasive breast cancer: HR, 0.24 (95% CI, 0.15-0.40) | Effective (ER+ only) | Martino 200422                     |
| ORGAN SYSTEM | COHORT | SAMPLE SIZE | INTERVENTION × DURATION | PRIMARY EFFICACY MEASURE(S) | EFFECT OF INTERVENTION ON RISK | AUTHOR AND YEAR OF PUBLICATION(S) |
|--------------|--------|-------------|-------------------------|----------------------------|--------------------------------|-----------------------------------|
| Breast (continued) | Postmenopausal women with CHD aged ≥35 y (RUTH) | 10,101 |Raloxifene 60 mg/d or placebo × median of 5.6 y | Invasive breast cancer: HR, 0.56 (95% CI, 0.38-0.83) | Effective | Barrett-Connor 2006<sup>23</sup> |
| | Women with low BMD ages 59-80 y (PEARL) | 8556 | Lasfoxifene 0.25 or 0.5 mg/d or placebo × 5 y | At 0.5 mg/d dose: Total breast cancer: HR, 0.21 (95% CI, 0.08-0.53); ER+ invasive breast cancer: HR, 0.17 (95% CI, 0.05-0.57) | Effective | LaCroix 2010<sup>24</sup> |
| | Women with low BMD (the Generations Study) | 9354 | Arzoxifene 20 mg/d or placebo × 4 y | Incidence of invasive breast cancer: HR, 0.44 (95% CI, 0.26-0.76; *P* < .001) | Effective | Cummings 2011<sup>26</sup> |
| Cervix | Women with CIN II and III | 301 | Cervical caps with all-trans retinoic acid 1 ml of 0.372% vs placebo × 8 mo (periodically) | CIN II: Complete histologic regression, 59% increase (*P* = .041); CIN III, regression (no difference) | Effective (borderline) | Meyskens 1994<sup>31</sup> |
| | Women with prevalent koilocytic atypia, CIN I or II | 331 | Folic acid 5 mg/d vs placebo × 6 mo | Cytologic or colposcopic CIN, no significant improvement | Null | Childes 1995<sup>32</sup> |
| | Women ages 16-23 y | 2392 | HPV type 16 (HPV-16) virus-like particle vaccine, 40 mcg/dose vs placebo × 3 with 17.4 mo follow-up | HPV-16-related CIN incidence: Rx vs placebo, 0 vs 9 cases (*P* < .001) | Effective | Koutsy 2002<sup>33</sup> |
| | Women with CIN II or III | 114 | 9-cis-Retinoic acid 25 mg/d vs 50 mg/d vs placebo × 12 wk | CIN regression rates: Placebo, 32%; low dose, 32%; high dose, 36%; no significant differences | Null | Alvarez 2003<sup>34</sup> |
| | 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 placebo × 4 d with outcomes at 12 wk | CIN complete regression rates: Placebo, 47%; low dose, 56%; moderate dose, 50%; high dose, 49%; no significant differences (*P* = .28) | Null | Ruffin 2004<sup>35</sup> |
| | Women not previously infected with HPV-16 or HPV-18 | 12,167 | HPV-6/HPV-11/HPV-16/HPV-18 vaccine vs placebo (3 doses of vaccine on d 0, 2 mo, and 6 mo) | HPV-16/HPV-18-related grade 2 or 3 CIN lesions, adenocarcinoma, or HPV-16/HPV-18-related cervical cancer; vaccine efficacy, 98% (95% CI, 86%-100%) | Effective | FUTURE II Study Group 2007<sup>36</sup> |
| ORGAN SYSTEM      | COHORT                                                                 | SAMPLE SIZE | INTERVENTION × DURATION | PRIMARY EFFICACY MEASURE(S)                                                                                     | EFFECT OF INTERVENTION ON RISK | AUTHOR AND YEAR OF PUBLICATION(S) |
|-------------------|------------------------------------------------------------------------|-------------|-------------------------|---------------------------------------------------------------------------------------------------------------|-------------------------------|-----------------------------------|
| 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 mo | OR of a normal esophagus at the conclusion of treatment, 0.85 (95% CI, 0.60-1.21)                           | Null                          | Munoz 1985, 1987                  |
|                   | Residents of Linxian, China ages 40-69 y 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 y | Esophageal cancer incidence with riboflavin + niacin: RR, 0.86 (95% CI, 0.74-1.01); esophageal cancer mortality with riboflavin + niacin: RR, 0.90 (95% CI, 0.73-1.11), with BC + vitamin E + selenium: RR, 0.96 (95% CI, 0.78-1.18) | Null                          | Bot 1993                         |
|                   | Residents of Linxian, China with esophageal dysplasia                  | 3318        | Multivitamin supplement (containing 14 vitamins and 12 minerals) vs placebo × 5.25 y | Esophageal/gastric cardia death: RR, 0.92 (95% CI, 0.67-1.28)                                               | Null                          | Li 1993                          |
|                   | Residents of Linxian, China with mild to moderate esophageal dysplasia  | 238         | Selenomethionine 200 μg/d and/or celecoxib 200 mg bid × 10 mo | Selenomethionine: Trend toward increased dysplasia regression (43% vs 32%) and decreased dysplasia progression (14% vs 19%; P = .08); significant effect on dysplasia grade in those with mild dysplasia (P = .02), but not in those with moderate dysplasia (P = 1.00); Celecoxib: No effect on dysplasia grade overall (P = .78) or by baseline histologic grade | Null                          | Limburg 2005                     |
|                   | High-grade Barrett dysplasia                                           | 208         | Porfimer sodium 2 mg/kg (followed by photodynamic light therapy) + omeprazole vs omeprazole × 2.36 y | ≥CR3 (major response) in 77% vs 39% (P < .001); CR1 (complete response) in 52% vs 7% (P < .001); cancer free at 24 mo, 83% vs 53% (P = .0014) | Effective                     | Axcan Pharma US Inc. 2003         |
|                   | Patients with Barrett esophagus and low-grade or high-grade dysplasia   | 100         | Celecoxib 200 mg bid × 48 wk | No significant difference in proportion of biopsy samples with dysplasia or cancer in either the low-grade group (median change with celecoxib, −0.09 [IQR, −0.32 to 0.14] with placebo, −0.07 [IQR, −0.26 to 0.12]; P = .64), or in the high-grade group (median change with celecoxib, 0.12 [IQR, −0.31 to 0.55] with placebo, 0.02 [IQR, −0.24 to 0.28]; P = .88) | Null                          | Heath 2007                       |
| Colorectum        | FAP with prevalent adenomas                                            | 10 (Cross-over design) | Sulindac 300 mg/d vs placebo × 4 mo | CR or near complete adenoma regression: Sulindac vs placebo, 9 vs 0 (increase in 5, stable disease in 2, relative reduction in 2; P<.01) | Effective                     | Labayle 1991                    |
|                   | FAP with prevalent adenomas                                            | 22          | Sulindac 150 mg bid vs placebo × 9 mo | CR polyp number, 56% reduction (P = .014); CR polyp diameter, 65% reduction (P<.001) | Effective                     | Giardiello 1993                 |
| ORGAN SYSTEM | COHORT | SAMPLE SIZE | INTERVENTION & DURATION | PRIMARY EFFICACY MEASURE(S) | EFFECT OF INTERVENTION ON RISK | AUTHOR AND YEAR OF PUBLICATION(S) |
|--------------|--------|-------------|--------------------------|-----------------------------|-------------------------------|----------------------------------|
| Colorectum (continued) | FAP with prevalent adenomas | 24 | Sulindac vs placebo × 6 mo | CR polyp number, significantly reduced ($P = 0.01$); duodenal polyp number, trend toward reduction ($P = 0.12$) | Effective | Nugent 1995<sup>48</sup> |
|          | US male physicians | 22,071 | Aspirin 325 mg/qod vs BC 50 mg/d vs both vs neither × 5 y | 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) | Null | Gann 1993<sup>49</sup> |
|          | FAP with prevalent adenomas | 77 | Celecoxib 200 bid vs 400 bid vs placebo × 6 mo | Mean no. of adenomas, 28% reduction ($P < 0.001$); polyp burden, 30.7% reduction ($P < 0.001$)<sup>a</sup> | Effective | Steinach 2000<sup>51</sup> |
|          | Genotype and phenotype: FAP patients ages 8-25 y | 41 | Sulindac 75-150 mg bid vs placebo × 48 mo | Adenoma incidence: Sulindac vs placebo, 43% vs 55% ($P = 0.54$); mean no. or size of adenomas, no significant differences | Null | Giardiello 2002<sup>52</sup> |
|          | Recent resected adenoma | 1121 | Aspirin 81 mg/d vs 325 mg/d vs placebo × 3 y | Adenoma recurrence: 81 mg: RR, 0.81 (95% CI, 0.69-0.98); 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<sup>53</sup> |
|          | Resected early stage CRC | 635 | Aspirin 325 mg/qod vs placebo × 3 y | 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); $P = 0.022$<sup>a</sup> | Effective | Sandler 2003<sup>54</sup> |
|          | Recent resected adenoma | 272 | Lysine acetylsalicylate 160-300 mg/d vs placebo × 1 y, lysine acetylsalicylate 160-300 mg/d vs placebo × 4 y | Adenoma recurrence: RR, 0.73 (95% CI, 0.52-1.04; $P = 0.08$); secondary analysis of large adenomas, 83% reduction ($P = 0.01$) | Null (effective in secondary analysis of large adenomas) | Benamouzig 2013<sup>55</sup> |
|          | US women aged ≥45 y, initially without history of cancer, CVD, or other major chronic illness | 39,876 | Aspirin 325 mg/qod vs placebo × 5 y | CRC incidence: RR, 0.97 (95% CI, 0.77-1.24) | Null (effective at 18-y follow-up) | Cook 2003<sup>57</sup> |
|          | Meta-analysis of cardiovascular trials reporting cancer endpoints | 7588 | UK-TIA: Aspirin 300-500 mg/d vs placebo × 1.7 y; British Doctors’ Aspirin Trial: Aspirin 300-1500 mg/d vs no aspirin × 5.6 y | CRC incidence: UK-TIA: HR, 0.74 (95% CI, 0.56-0.97); British Doctors’ Aspirin Trial, effect seen after 10-y latency | Effective (after 10-y latency) | Rossman 2007<sup>58</sup> |
| ORGAN SYSTEM               | COHORT                                      | SAMPLE SIZE | INTERVENTION × DURATION                              | PRIMARY EFFICACY MEASURE(S)                                                                 | EFFECT OF INTERVENTION ON RISK | AUTHOR AND YEAR OF PUBLICATION(S) |
|---------------------------|---------------------------------------------|-------------|-----------------------------------------------------|---------------------------------------------------------------------------------------------|-------------------------------|----------------------------------|
| Colorectum (continued)    | Recent resected adenoma                     | 375         | Oral DFMO 500 mg and sulindac 150 mg/d or matched placebos × 36 mo | Recurrence of one or more adenomas: RR, 0.30 (95% CI, 0.18-0.49; P < .001); advanced adenomas: RR, 0.085 (95% CI, 0.011-0.65; P < .001); multiple adenomas: RR, 0.055 (95% CI, 0.0075-0.41; P < .001) | Effective                      | Meyskens 200862                  |
|                           | Recent resected adenoma                     | 939         | Aspirin 300 mg/d and folate supplements 0.5 mg/d vs placebo in 2 × 2 factorial design × 3 y | Adenoma recurrence: RR, 0.79 (95% CI, 0.63-0.99); advanced adenoma: RR, 0.63 (95% CI, 0.43-0.91) | Effective                      | Logan 200863                    |
|                           | Meta-analysis of cardiovascular trials reporting cancer endpoints | 14,033     | Aspirin (75-1200 mg/d) vs control × 6 y (mean duration of treatment) | CRC incidence: HR, 0.76 (95% CI, 0.60-0.96; P = .02); CRC mortality: HR, 0.65; (95% CI, 0.48-0.88; P = .005) | Effective                      | Rothwell 201064                  |
|                           | FAP patients, ages 10-21 y (CAPP-1)         | 206         | Aspirin 600 mg/d and/or resistant starch (30 g/d) vs placebo × 1-12 y | Polyp count: Aspirin: RR, 0.77 (95% CI, 0.54-1.11); mean size of largest observed polyp, 3.0 mm in aspirin-treated group vs 6.0 mm in placebo group (P = .02) | Null (effective for size of largest observed polyp) | Burn 201165                      |
|                           | Carriers of Lynch syndrome (CAPP-2)         | 937         | Aspirin 600 mg or aspirin placebo or 30 g resistant starch or starch placebo, for up to 4 y | Time to first CRC: HR, 0.63 (95% CI, 0.35-1.13; P = .12); for those completing 2 y of intervention: HR, 0.41 (95% CI, 0.19-0.86; P = .02); IRR, 0.37 (95% CI, 0.18-0.76; P = .008) | Null (effective for those completing 2 y of intervention) | Burn 201166                      |
|                           | Hormone-replacement therapy                |             |                                                     |                                                                                             |                               |                                  |
|                           | Postmenopausal women with coronary artery disease | 2763      | Conjugated estrogens 0.625 mg/d + medroxyprogesterone acetate 2.5 mg/d vs placebo × 4 y | CRC incidence: No significant difference between intervention and placebo groups; unadjusted intention-to-treat: HR, 0.81 (95% CI, 0.46-1.43); adjusted as-treated: HR, 0.58 (95% CI, 0.25-1.33) | Null                           | Hulley 200267                   |
|                           | Healthy postmenopausal women                | 16,608     | Conjugated equine estrogens 0.625 mg/d + medroxyprogesterone acetate 2.5 mg/d vs placebo × 5.2 y | CRC incidence: RR, 0.63 (95% CI, 0.43-0.92) | Effective                      | Rosouw 200268                   |
|                           |                                              |             |                                                     | CRC stage at diagnosis: Rate of regional or metastatic disease in hormone group (76.2%) vs placebo (48.5%; P = .004) |                               | Chlebowski 200469               |
|                           | Healthy postmenopausal women with hysterectomy | 10,738     | Conjugated equine estrogen 0.625 mg/d vs placebo × 7.1 y | CRC incidence: RR, 1.08 (95% CI, 0.75-1.55) | Null                           | Anderson 200420                 |
|                           |                                              |             |                                                     | Survival after CRC diagnosis: RR, 1.34 (95% CI, 0.58-3.19) |                               | Ritenbaugh 200811               |
|                           | Micronutrients/dietary agents               |             |                                                     |                                                                                             |                               |                                  |
|                           | Recent resected adenoma                     | 864         | BC 25 mg/d vs vitamin C 1 g/d + vitamin E 400 mg/d vs both vs placebo × 4 y | Adenoma recurrence: BC: RR, 1.01 (95% CI, 0.85-1.20); vitamins C + E: RR, 1.08 (95% CI, 0.91-1.29) | Null                           | Greenberg 199422                 |
| ORGAN SYSTEM            | COHORT                                          | SAMPLE SIZE | INTERVENTION × DURATION | PRIMARY Efficacy MEASURE(S)                                                                 | EFFECT OF INTERVENTION ON RISK                                      | AUTHOR AND YEAR OF PUBLICATION(S) |
|-------------------------|-------------------------------------------------|-------------|--------------------------|-------------------------------------------------------------------------------------------|---------------------------------------------------------------------|-----------------------------------|
| Colorectum (continued)  | Patients with prior skin cancer                 | 1312        | Selenium 200 μg/d vs placebo × 6.4 y | CRC incidence: RR, 0.42 (95% CI, 0.18-0.95; P = .03)                                       | Effective                                                           | Clark 199664                       |
|                         | Recent resected adenoma                          | 913         | Calcium carbonate 3 g/d vs placebo × 4 y | Adenoma recurrence: Adjusted RR, 0.85 (95% CI, 0.74-0.98; P = .03)                         | Effective                                                           | Baron 199975                       |
|                         | Recent resected adenoma                          | 1429        | Wheat bran fiber 13.5 g/d vs 2 g/d × 5 y | Adenoma recurrence: Adjusted OR, 0.88 (95% CI, 0.70-1.11; P = .28)                         | Null                                                               | Alberts 200076                     |
|                         | Recent resected adenoma                          | 2079        | Intensive low-fat, high-fiber, high fruits and vegetable diet vs no intervention × 4 y | Adenoma recurrence: RR, 1.00 (95% CI, 0.90-1.12)                                          | Null                                                               | Schatzkin 200077                   |
|                         | Recent resected adenoma                          | 665         | Calcium gluconolactate/carbonate 2 g/d vs ispaghula husk 3.5 g/d vs placebo × 3 y | Adenoma recurrence: Calcium: OR, 0.66 (95% CI, 0.38-1.17; P = .16); fiber: OR, 1.67 (95% CI, 1.01-2.76; P = .042) | Null (calcium), deleterious (fiber)                                   | Bonithon-Kopp 200078               |
|                         | Postmenopausal women                             | 36,282      | Elemental calcium 500 mg as calcium carbonate with 200 IU vitamin D3 bid vs placebo × 7 y | CRC incidence: No significant difference between intervention and placebo groups (HR, 1.08; 95% CI, 0.86-1.34; P = .51) | Null                                                               | Wactawski-Wende 200679             |
|                         | Men aged ≥ 50 y (African-American) or ≥ 55 y (Caucasian) with serum PSA level ≤ 4 ng/ml and a DRE “not suspicious for prostate cancer” | 35,533      | Oral selenium (200 μg/d from L-selenomethionine) and matched vitamin E placebo, vitamin E (400 IU/d of all-rac AT acetate) and matched sodium placebo, selenium + vitamin E, or placebo + placebo × 7-12 y | CRC incidence: No significant difference between intervention and placebo groups (HR, 1.08; 95% CI, 0.86-1.34; P = .51) | Null                                                               | Lippman 200980                     |
|                         | FAP patients aged ≥ 18 y who had previously undergone colectomy with ileorectal anastomosis | 58          | Enteric-coated formulation of EPA as the free fatty acid EPA-FFA, 2 g/d vs placebo × 6 mo | No. of polyps: 22.4% reduction in EPA group (P = .012); polyp size: 29.8% reduction in sum of polyp diameters in EPA group (P = .027) | Effective                                                           | West 201081                        |
|                         | Recent resected adenoma                          | 2259        | Vitamin D3 1000 IU/d, calcium 1200 mg/d, both, or neither × 3-5 y | Adenoma recurrence: Vitamin D3 alone: RR, 0.97 (95% CI, 0.88-1.08); calcium alone: RR, 0.95 (95% CI, 0.85-1.08); vitamin D3 + calcium vs calcium alone: RR, 0.99 (95% CI, 0.86-1.13) | Null                                                               | Baron 2014 (Presented at AACR Annual Meeting, Abstract CT335)82 |
|                         | Bladder Superficial bladder cancer               | 37          | BCG 120 mg intravesical and 5 mg percutaneous once weekly × 6 wk after TUR vs TUR alone | Tumor recurrence rate, 22% in TUR + BCG groups vs 42% in TUR-alone group (P = .029)          | Effective                                                           | Lamm 198083                        |
|                         | Recurrent superficial carcinoma of the bladder   | 88          | BCG 120 mg intravesical and 5 mg percutaneous once weekly × 6 wk after TUR vs TUR alone | No. of patients showing reduction in no. of recurrent tumors: 43 in TUR + BCG groups vs 27 in TUR-alone group (P = .001) | Effective                                                           | Pinsky 198584                      |
| ORGAN SYSTEM  | COHORT                                                                 | SAMPLE SIZE | INTERVENTION × DURATION | PRIMARY EFFICACY MEASURE(S)                                                                 | EFFECT OF INTERVENTION ON RISK | AUTHOR AND YEAR OF PUBLICATION(S) |
|---------------|------------------------------------------------------------------------|-------------|--------------------------|-----------------------------------------------------------------------------------------------|-------------------------------|----------------------------------|
| Bladder (continued) | Recurrent superficial transitional cell carcinomas of the bladder | 86          | BCG 120 mg intravesical and 5 mg percutaneous once weekly × 6 wk after TUR vs TUR alone | Percentage with disease progression: 53% in TUR + BCG groups vs 95% in TUR-alone group       | Effective                      | Herr 198886                       |
|               |                                                                        |             |                          | 10-y progression-free rate, 61.9% in TUR + BCG groups vs 37% in TUR-alone group; 10-y disease-specific survival rate, 75% in TUR + BCG groups vs 55% in TUR-alone group (P = .03) |                               |                                  |
| Superficial transitional cell carcinoma |                                                                        | 660         | BCG: intravesical and percutaneous, induction and maintenance × 3 y vs induction alone | Median recurrence-free survival, 35.7 mo vs 76.8 mo (P < .0001)                            | Effective                      | Lamm 20007                         |
| BCG-refractory CIS of the bladder |                                                                        | 90          | Valrubicin 800 mg intravesical once weekly × 6 wk (open-label, noncomparative, pivotal phase 3 study) | Percentage complete responders, 21% disease-free at 3 mo and 6 mo follow-up                    | Effective                      | Steinberg 200218                   |
| Recurrent CIS after failed multiple courses of intravesical therapy, including at least one course of BCG (pivotal phase 3) |                                                                        | 90          | Valrubicin 800 mg once weekly × 6 wk (open-label, noncomparative study) | Pivotal phase 3 study; Percentage complete responders, 18% disease free at primary disease evaluation and 3 mo follow-up | Effective                      | Dinney 201389                      |
| CIS alone or with papillary disease (Ta/T1) and failed BCG, BCG-intolerant, or BCG was contraindicated (A9303) |                                                                        | 80          | Valrubicin 800 mg of once weekly × 6-9 wk | A9303 phase 2/3 study: Percentage complete responders, 18%                                    | Effective                      | Dinney 201389                      |
| Skin          | Resected NMSC                                                          | 1805        | BC 50 mg/d vs placebo × 5 y | Secondary NMSCs: RR, 1.05 (95% CI, 0.91-1.22)                                                   | Null                          | Greenberg 199090                   |
|               | Resected BCC                                                           | 981         | Isotretinoin 10 mg/d vs placebo × 3 y | Percentage of patients with incident BCCs, no significant difference; annual rate of incident BCCs, no significant difference | Null                          | Tangrea 19999                        |
|               | Resected BCC or SCC                                                    | 525         | Retinol 25,000 IU/d vs isotretinoin 5-10 mg/d vs placebo × 3 y | Time to first skin cancer, no significant difference; no. of incident skin cancers, no significant difference | Null                          | Levine 199792                      |
|               | Resected BCC or SCC                                                    | 1312        | Selenium 200 mcg/d vs placebo × mean 4.5 y | BCC incidence: RR, 1.10 (95% CI, 0.95-1.28); SCC incidence: RR, 1.14 (95% CI, 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); significant difference; prostate cancer incidence: RR, 0.37 (P = .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, 199874, 93           |
|               | Resected AKs and/or skin cancers                                       | 2297        | Retinol 25,000 IU/d vs placebo × 5 y | SCC incidence, reduced in those with prior AKs (P = .04); otherwise no significant effects | Effective (borderline; in those with prior AKs)                                              | Moon 199794                      |
| Healthy male physicians ages 40-84 y |                                                                        | 22,071      | BC 50 mg qod vs placebo × 12 y | NMSC incidence: RR, 0.98 (95% CI, 0.92-1.05); BCC incidence: RR, 0.99 (95% CI, 0.92-1.06); SCC incidence: RR, 0.97 (95% CI, 0.84-1.13) | Null                          | Frieling 200095                    |
| ORGAN SYSTEM | SAMPLE SIZE |cohorts | Nº | intervention x duration | Primary Efficacy Measure(s) | Effec of Intervention on Risk of Treatment |Author and Year of Publication(s) |
|---------------|-------------|---------|----|--------------------------|----------------------------|-----------------------------------------|----------------------------------|
| Skin (continued) | 50 | Provenvent | 3 | Topical T4N5 liposome lotion vs placebo | 3 mo | Annual rate of new AKs: Rx vs placebo, 8.2 vs 25.9 (yielding a significant difference of 17.7; 95% CI, 11.8-26.5); annual rate of BCCs: Rx vs placebo, 3.8 vs 5.4 (yielding a difference of 1.6; 95% CI, 0.8-2.4) | Yarosh 2001 |
| | | | | | | | |
| | | Prevalent AKs | 36 | Topical 20% aminolevulinic acid hydrochloride with fluorescent blue light vs vehicle | 1 treatment | AK clearance: Treated vs control, 88% vs 6% | Jeffes 2001 |
| | | | | | | | |
| | | | | | | | |
| | | Healthy adults with 4-8 AKs on face or balding scalp vs vehicle | 480 | Imiquimod 5% cream vs placebo | once daily for 2 d/wk, 16 wk | Complete clearance rate (proportion at the 8-wk posttreatment visit with a count of 0 clinically visible AK lesions), 45.1% vs 3.2% (P < .001) | Lebwohl 2004 |
| | | | | | | | |
| | | Patients aged ≥ 18 y with AKs | 70 | Oral acetretin 25 mg/d for 5 d/wk vs placebo | 4.5 y | Tretinoin vs control: BCC at 5 y, 53% vs 54% (OR, 0.41; 95% CI, 0.19-0.98; P = 0.03); cSCC at 5 y, 28% vs 31% (OR, 0.81; 95% CI, 0.57-1.15; P = 0.21) | Bailey 2010 |

**TABLE 3. Continued**
| ORGAN SYSTEM        | COHORT                                      | SAMPLE SIZE | INTERVENTION × DURATION | PRIMARY EFFICACY MEASURE(S)                                                                 | EFFECT OF INTERVENTION ON RISK | AUTHOR AND YEAR OF PUBLICATION(S) |
|---------------------|---------------------------------------------|-------------|-------------------------|------------------------------------------------------------------------------------------------|-------------------------------|-----------------------------------|
| Skin (continued)    | Basal cell nevus syndrome patients          | 42          | Vismodegib 150 mg/d vs placebo × 18 mo | Comparative rate of appearance of new BCCs that were surgically eligible: 2 vs 29 BCCs per patient per y (P < .001) | Effective                      | Tang 2012[108]                    |
| Oral/head & neck    | Oral leukoplakia                            | 44          | Isotretinoin 1-2 mg/kg/d vs placebo × 3 mo | Leukoplakia regression (major size reduction) in 85% (statistically significant; P = .0002); reversed dysplasia in 81% (P = .01) | Effective                      | Hong 1986[109]                    |
|                     | Resected HNSCC                              | 103         | Isotretinoin 50-100 mg/m²/d vs placebo × 12 mo | Second primary tumors reduced 83% (P = .005) | Effective                      | Hong 1990[110]                    |
|                     | Oral leukoplakia (mucosal hyperplasia or dysplasia) | 70 (59) | Isotretinoin 1.5 mg/kg/d × 3 mo; responders randomized to Isotretinoin 0.5 mg/kg/d vs BC 30 mg/d × 9 mo | Leukoplakia regression: Isotretinoin vs BC, 92% vs 45% response (P < .001) | Effective                      | Lippman 1993[111]                 |
|                     | Stage III HNSCC definitively treated with XRT or surgery | 1190 | Isotretinoin (30 mg/d) vs placebo × 3 y (and followed for an additional 4 y) | Second primary tumors not significantly reduced (HR, 1.06; 95% CI, 0.83-1.35); survival not significantly increased (HR, 1.03; 95% CI, 0.81-1.32) | Null                           | Khuri 2006[112]                   |
|                     | Resected HNSCC                              | 316         | Etretinate 25-50 mg/d vs placebo × 24 mo | Second primary tumors not significantly reduced | Null                           | Bull 1994[113]                    |
|                     | Resected HNSCC or lung cancer               | 2592        | Retinyl palmitate 150-300 IU/d vs N-acetylcysteine 600 mg/d vs both vs neither × 2 y | Second primary tumors not significantly reduced; OS or EFS not significantly reduced | Null                           | van Zandwijk 2000[114]            |
|                     | Patients with OPLs (noninferiority trial)   | 162         | 13cRA (0.5 mg/kg/d orally for 1 y followed by 0.25 mg/kg/d orally for 2 y) or BC (50 mg/d orally) plus RP (25,000 U/d orally) for 3 y and later (by protocol revision) to 13cRA or RP-alone × 3 y and followed for 2 additional y | OPL clinical response rate at 3 mo: Combined rate for BC + RP arm and RP-alone arm (32.5%) not statistically equivalent to that of the 13cRA arm (48.1%); oral cancer-free survival at 5 y: For all 3 arms: 13cRA, 78%; BC + RP, 84%; RP, 82% (P = .66 for the overall comparison; not significantly different) | Equivalence of RP + BC or RP alone with low-dose 13cRA not established | Papadimitrioupolou, 2009[115]      |
| Lung                | Male smokers ages 50-69 y                   | 29,133      | AT 50 mg/d vs BC 20 mg/d vs both vs neither × 5-8 y | Primary lung cancer incidence: AT, 2% reduction (95% CI, 0-4%); BC, 18% increase (95% CI, 3-36%); secondary analyses, prostate cancer incidence: AT, 32% reduction (statistically significant); BC, 23% increase (NS) increase; cancer mortality: AT, 41% reduction (statistically significant); BC, 15% increase (NS) | Deleterious                     | ATBC 1994[116]                    |
|                     | Smokers, former smokers, and workers exposed to asbestos | 18,314     | AT 50 mg/d vs BC 20 mg/d vs both vs neither × 5-8 y with 6-8 y of additional follow-up | With 6-8 y 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) | Deleterious                     | Virtamo 2003[117]                 |
|                     | Male physicians ages 40-84 y                | 22,071      | BC 50 mg qod vs ASA 325 mg qod vs both vs placebo × 12 y | BC results (ASA terminated early): Cancer incidence: RR, 0.98 (95% CI, 0.91-1.06); secondary analyses: Lung cancer incidence: Current smokers: RR, 0.90 (95% CI, 0.58-1.40); former smokers: RR, 1.00 (95% CI, 0.62-1.61); never smokers: RR, 0.78 (95% CI, 0.34-1.79); cancer mortality: RR, 1.02 (95% CI, 0.89-1.18) | Null                           | Hennelers 1996[118]               |
| ORGAN SYSTEM                     | COHORT                                                                 | SAMPLE SIZE | INTERVENTION × DURATION | PRIMARY EFFICACY MEASURE(S)                                                                 | EFFECT OF INTERVENTION ON RISK                                      | AUTHOR AND YEAR OF PUBLICATION(S) |
|----------------------------------|-------------------------------------------------------------------------|-------------|-------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------|----------------------------------|
| Lung (continued)                 | Resected NSCLC or head & neck cancer                                    | 2592        | RP 300,000 IU/d × 1 y, then 150,000 IU/d × 1 y vs NAC 600 mg/d × 2 y vs both vs no intervention | 5-Y OS: 71% vs 72% (NAC vs no NAC); 70% vs 73% (RP vs no RP); no effect on EFS or second primary tumor | Null                              | van Zandwijk 2000114             |
|                   | Resected stage I NSCLC                                                 | 1166        | Isotretinoin 30 mg/d vs placebo × 3 y | SPT: 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) | Null                              | Lippman 2001120                  |
|                   | Resected stage I NSCLC aged ≥18 y                                       | 1772        | Selenium 200 μg/d vs placebo × 48 mo (selenized yeast) | SPT: Lung cancer SPT: 1.62 vs 1.30 per 100 person-years (selenium vs placebo); overall SPT: 3.54 vs 3.39 per 100 person-years (selenium vs placebo; P = .294); 5-Y DFS: 74.4% vs 79.6% (selenium vs placebo; P = .068); 5-Y OS: 76.8% vs 79.9% (selenium vs placebo; P = .154) | Null                              | Karp 2013121                     |
| Prostate            | Men aged >50 y                                                          | 18,882      | Finasteride 5 mg/d vs placebo × 7 y | 7-Y period prevalence: 24.8% reduction (statistically; 95% CI, 18.6-30.6; P < .001); Gleason grade 7-10 more common in the treated group (P < .001; statistically significant) | Effective (but increased high-grade tumors)                        | Thompson 2003122                |
|                   | Men aged ≥50 y (African American) or ≥55 y (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-AT acetate) with matched selenium placebo; both agents, or both matched placebos × a minimum of 7 y and a maximum of 12 y | HRs for prostate cancer in 2008: 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 | Null                              | Lippman 2009120                  |
|                   | Men ages 50-75 y with a PSA 2.5-10.0 ng/mL and 1 negative prostate biopsy within 6 mo before enrollment | 8231        | Dutasteride 0.5 mg/d × 4 y | Incident prostate cancer: RR, 23% reduction (95% CI, 15.2-29.8; P < .001); AR, 5% decrease; AR for high-grade tumors, ≤0.5% increase | Effective (but increased high-grade tumors)                        | Andriole, 2010124               |
| Stomach (gastric, noncardia)     | Residents of Linxian, China ages 40-69 y 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 y | Stomach cancer incidence: RR, 0.79 (95% CI, 0.64-0.99) with BC + vitamin E + selenium | Effective (borderline; BC + vitamin E + selenium)                  | Blot 1993125                    |
|                   | Residents of Narino, Columbia with precancerous lesions                | 852         | Anti-Helicobacter antibiotics and/or BC and/or ascorbic acid vs placebo × 6 y | Preneoplastic lesion regression: Anti-H. pylori antibiotics: RR, 4.8 (95% CI, 1.6-14.2); BC: RR, 5.1 (95% CI, 1.7-15.0); ascorbic acid: RR, 5.0 (95% CI, 1.7-14.4) | Effective                                                             | Correa 2000125                   |
| ORGAN SYSTEM                | COHORT                                                                 | SAMPLE SIZE | INTERVENTION × DURATION                                                                 | PRIMARY EFFICACY MEASURE(S)                                                                 | EFFECT OF INTERVENTION ON RISK                                                                 | AUTHOR AND YEAR OF PUBLICATION(S) |
|----------------------------|------------------------------------------------------------------------|-------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|----------------------------------|
| Stomach (gastric, noncardia) (continued) | Healthy carriers of H. pylori in Fujian Province, China                | 1630        | H. pylori eradication treatment (2-wk course of omeprazole 20 mg. combination of amoxicillin + clavulante potassium 750 mg. and metronidazole 400 mg. all bid) vs placebo | Gastric cancer incidence: No statistically significant difference between treatment vs placebo after 7.5 y of follow-up; subgroup analysis in H. pylori carriers without precancerous lesions: gastric cancer incidence: \( P = .02 \) (Kaplan-Meier analysis) | Null (Effective in subgroup analysis of those without precancerous lesions)                      | Wong 2004^2,6                        |
| Adults ages 35-64 y from Shandong Province, China | Factorial design: Amoxicillin + omeprazole for 2 wk; vitamin C + vitamin E + selenium for 7.3 y (vitamin supplement); aged garlic extract + steam-distilled garlic oil for 7.3 y (garlic supplement) | 3365        | ORs for combined endpoint of dysplasia or gastric cancer: 1.13 (95% CI, 0.89-1.44; \( P = .32 \)) for H. pylori treatment, 1.10 (95% CI, 0.89-1.32; \( P = .39 \)) for vitamin supplement, 0.98 (95% CI, 0.79-1.22; \( P = .86 \)) for garlic supplement; ORs for second combined endpoint of severe chronic atrophic gastritis, intestinal metaplasia, dysplasia, or gastric cancer: 0.77 (95% CI, 0.62-0.95; \( P = .016 \)) for H. pylori treatment, 1.32 (1.12-1.57; \( P = .001 \)) for vitamin supplement, 0.99 (95% CI, 0.84-1.18; \( P = .94 \)) for garlic supplement | H. pylori, effective (second combined endpoint and gastric cancer incidence at 15 y follow-up); vitamin supplement, effective (second combined endpoint only); garlic supplement, null | You 2006^2,7                        |
| Adults ages 35-64 y from Shandong Province, China with H. pylori infection and advanced gastric lesions | Factorial design: Anti-H. pylori treatment (omeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg bid) for 7 d and celecoxib (200 mg bid) for 24 mo | 1024        | ORs for regression of lesions: 1.72 (95% CI, 1.07-2.76; \( P = .002 \)) for H. pylori treatment, 0.81 (95% CI, 0.54-1.22; \( P = .32 \)) for vitamin supplement, 0.80 (95% CI, 0.53-1.20; \( P = .28 \)) for garlic supplement; HRs for gastric cancer mortality: 0.67 (95% CI, 0.36-1.28; \( P = .22 \)) for H. pylori treatment, 0.55 (95% CI, 0.29-1.03; \( P = .06 \)) for vitamin supplement, 0.85 (95% CI, 0.35-1.20; \( P = .17 \)) for garlic supplement | Celecoxib, effective; H. pylori, effective; H. pylori followed by celecoxib, null | Ma 2012^3,8                         |
| Liver Chronic active hepatitis C with cirrhosis | Interferon-\( \alpha \) 6 MU tiw vs symptomatic Rx × 12-24 wk with 2-7 y follow-up | 90          | Primary cancer incidence: RR, 0.067 (95% CI, 0.009-0.53; \( P = .01 \)) | Effective | Nishiguchi 1995^3,90 |
| Prior resected or alcohol-ablated liver cancer | Polyprenolic acid 600 mg/d vs placebo × 12 mo | 89          | Second primary cancer incidence: RR, 0.31 (95% CI, 0.12-0.78)^* | Effective | Muto 1996^3,11 |
| Male patients with chronic hepatitis B infection | Interferon vs interferon with prednisolone priming vs placebo × 12 wk | 101         | Cumulative primary cancer incidence, 87% reduction (\( P = .013 \)^* | Effective | Lin 1999^3,2 |
| Compensated hepatitis C-related cirrhosis | Interferon × 2b 3 MU tiw vs no treatment × 48 wk | 99          | Primary cancer incidence, no significant effect | Null | Valli 1999^3,3 |
| Chronic hepatitis B with cirrhosis or advanced fibrosis | Lamivudine (100 mg/d) vs placebo × 5 y | 651         | HCC incidence: HR, 0.49 (95% CI, 0.25-0.99; \( P = .047 \)) | Effective (borderline) | Liaw 2004^3,4 |
### TABLE 3. Continued

| ORGAN SYSTEM | COHORT | SAMPLE SIZE | INTERVENTION × DURATION | PRIMARY EFFICACY MEASURE(S) | EFFECT OF INTERVENTION ON RISK | AUTHOR AND YEAR OF PUBLICATION(S) |
|--------------|--------|-------------|-------------------------|----------------------------|--------------------------------|----------------------------------|
| Overall cancer incidence and mortality | Residents of Linxian, China ages 40-69 y 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 y | 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 | Effective (overall mortality [especially at 15-y follow-up] and cancer mortality at 15-y follow-up in subgroup analysis) | Biot 1993³³⁰³³¹ |
| | | | | 15-y follow-up: Overall mortality: HR, 0.95 (95% CI, 0.91-0.99; P = .009) with BC + vitamin E + selenium; overall mortality aged < 55 y: HR, 0.88 (95% CI, 0.82-0.95; P < .001) with BC + vitamin E + selenium; overall mortality aged ≥ 55 y: HR, 0.98 (95% CI, 0.93-1.03; P = .367) with BC + vitamin E + selenium; overall cancer mortality aged < 55 y: HR, 0.83 (95% CI, 0.76-0.95; P = .003) with BC + vitamin E + selenium; overall cancer mortality aged ≥ 55 y: HR, 1.02 (95% CI, 0.94-1.12; P = .976) with BC + vitamin E + selenium | Qiao 2009⁴³⁰⁴³¹ |
| | Healthy male physicians ages 40-84 y | 22,071 | BC 50 mg qod vs placebo × 12 y | Overall cancer incidence: RR, 0.98 (95% CI, 0.91-1.06); cancer mortality: RR, 1.02 (95% CI, 0.89-1.18) | Null | Hennekens 1996³³²³³³³³³⁴⁰⁴¹ |
| Physicians’ Health Study II (males aged ≤50 y) | 14,641 | Multivitamin (Centrum Silver) vs placebo × 11.2 y (median treatment and follow-up) | Overall cancer incidence: HR, 0.92 (95% CI, 0.86-0.998; P = .04) with BC; cancer mortality: HR, 0.88 (95% CI, 0.77-1.01; P = .07); overall mortality: HR, 0.94 (95% CI, 0.88-1.02; P = .13); no significant cancer site-specific findings | Null (borderline effective for overall cancer incidence) | Gaziano 2012³³⁵³³⁶³³⁷³³⁸³³⁹³⁴⁰³⁴¹ |

13cRA indicates 13-cis-retinoic acid; AACR, American Association for Cancer Research; AKs, actinic keratoses; AR, absolute risk; ASA, 5-aminosalicylate; AT, α-tocopherol; ATBC Alpha-Tocopherol Beta Carotene Study; BC, β-carotene; BCC, basal cell cancer; BCG, bacillus Calmette-Guérin; BMD, bone mineral density; bid, twice daily; CAAP, Colorectal Adenoma/Carcinoma Prevention Program; CHD, chronic heart disease; CI, confidence interval; CIN I, cervical intraepithelial neoplasia 1 (mild dysplasia); CIN II, cervical intraepithelial neoplasia 2 (moderate to marked dysplasia); CIN III, cervical intraepithelial neoplasia 3 (severe dysplasia to carcinoma in situ); CIS, carcinoma in situ; CORE, Continuing Outcomes Relevant to Evista; CR, complete response; CRC, colorectal cancer; cuSCC, cutaneous squamous cell cancer; CVD, cardiovascular disease; DCIS, ductal carcinoma in situ; DFMO, difluoromethylornithine; DRE, digital rectal examination; EFS, event-free survival; EPA-FFA, eicosapentaenoic acid-free fatty acid; ER, estrogen receptor-negative; ER+, estrogen receptor-positive; FAP, familial adenomatous polyposis; FUTURE, Females United to Unilaterally Reduce Endo/Ectocervical Disease; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell cancer; HPV, human papillomavirus; H. pylori; Helicobacter pylori; HR, hazard ratio; IBIS-I, First International Breast Cancer Intervention Study; IGR, interquartile range; IRR, incidence rate ratio; MORE, Multiple Outcomes of Raloxifene Evaluation; NAC, N-acetylcysteine; NCIC-MAP.3, National Cancer Institute of Canada Mammary Prevention 3 trial; NMSC, nonmelanoma skin cancer; NS, nonsignificant; NSABP-P1/BCPT, National Surgical and Adjuvant Breast and Bowel Project/Breast Cancer Prevention Trial; NSABP-P2/STAR, National Surgical and Adjuvant Breast and Bowel Project/Study of Tamoxifen and Raloxifene; NSAIDs, nonsteroidal anti-inflammatory drugs; NSCLC, nonsmall cell lung cancer; OPLs, oral premalignant lesions; qod, every other day; OR, odds ratio; OS, overall survival; PEARL, Postmenopausal Evaluation and Risk Reduction with Lasofoxifene; PR, progesterone receptor-positive; PSA, prostate-specific antigen; RP, retinyl palmitate; RR, relative risk; RUTH, Raloxifene Use for the Heart; Rx, prescription (treatment drug); SCC, squamous cell cancer; SELECT, Selenium and Vitamin E Cancer Prevention Trial; SPT, second primary tumor; TIA, transient ischemic attack; tiw, 3 times a week; TUR, transurethral resection; XRT, external-beam radiotherapy. *A phase 2B trial, but no phase 3 trial, was conducted for esophageal adenocarcinoma (EAC); the Aspirin Esomeprazole Chemoprevention Trial (AspECT) is ongoing and is expected to report results on esophageal adenocarcinoma. These results are statistically significant.
thromboembolic/cardiovascular events. In addition, its preventive effects degrade after 3 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 (ductal carcinoma in situ [DCIS]) breast cancers.\(^{18,19}\) Given that there appears to be a tradeoff between side effects and effectiveness over the long-term, the selection of tamoxifen versus raloxifene as a preventive therapy depends upon the patient. Because it is less likely to cause uterine cancer than is tamoxifen, raloxifene may be best for postmenopausal women at high risk of breast cancer with an intact uterus. However, in postmenopausal women without a uterus, tamoxifen may be the drug of choice, because it shows enhanced effectiveness over the long-term.

After those 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 that was developed for the treatment of osteoporosis, as a breast cancer-preventive agent in postmenopausal women with low bone mineral density.\(^{24,25}\) The results of that phase 3 clinical prevention trial showed a 79\% reduction in invasive breast cancer and an 83\% reduction in ER-positive breast cancer in patients who received lasofoxifene. A similar phase 3 prevention trial, known as the Generations Trial, reported a 56\% decrease in invasive breast cancers in postmenopausal women with low bone mineral density who received arzoxifene, a SERM that was developed to maintain bone density in patients with osteoporosis.\(^{26,27}\) Those trials indicated that both lasofoxifene and arzoxifene reduced the risk of nonvertebral and vertebral fractures; however, these third-generation SERMs, like raloxifene and tamoxifen, still increase the risk of venous thromboembolic events.\(^{24-27}\) To date, neither lasofoxifene nor arzoxifene has been approved for clinical use by the FDA.

A meta-analysis conducted by Cuzick and colleagues was recently published that included all 9 of the large-scale phase 3 SERM prevention trials.\(^{146}\) Their comparative analysis demonstrates that overall breast cancer incidence is decreased by SERMs, although this was because of 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 vs 798 events across 9 SERM trials; odds ratio [OR], 0.66; 95\% confidence interval [CI], 0.59-0.73) but increased endometrial cancer (105 vs 63 events across 9 SERM trials; hazard ratio [HR], 1.56; 95\% CI, 1.13-2.14) and venous thromboembolic events (375 vs 215 events across 9 SERM trials; OR, 1.73; 95\% CI, 1.47-2.05).\(^{146}\) Extended follow-up of the first International Breast Cancer Intervention Study (IBIS-I) trial, with a median follow-up of 16 years, did not identify any new late toxicities and demonstrated a substantially improved benefit-harm balance for tamoxifen over the long term.\(^{147}\) Unfortunately, none of the SERM-based preventive interventions decrease the risk of ER-negative breast cancer.

**Aromatase inhibitors.** Whereas SERMs modulate estrogenic activity, aromatase inhibitors (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 (eg, the Arimidex, Tamoxifen, Alone or in Combination [ATAC] trial\(^{148,149}\)) have demonstrated improved results with AIs compared with SERMs. Those positive results led to phase 3 trials testing the preventive efficacy of AIs (eg, exemestane and anastrozole) for the development of breast cancer in high-risk women.\(^{28-30,149}\) The first of the AI prevention trials to be reported was the National Cancer Institute of Canada Mammary Prevention 3 (NCIC-MAP3) trial in which postmenopausal women at high risk of breast cancer were treated daily with exemestane or placebo for 5 years.\(^{30}\) The results showed that exemestane reduced the 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 the incidence of ER-negative breast cancer. A second prevention trial testing the AI anastrozole in high-risk postmenopausal women demonstrated a 53\% reduction in the incidence of all breast cancer, a 50\% reduction in the incidence of invasive breast cancer, and a 58\% reduction in ER-positive breast cancer.\(^{29}\) As in the exemestane trial, no significant reduction in the incidence of ER-negative breast cancer was observed. 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 National Surgical and Adjuvant Breast and Bowel Project (NSABP) B-35 trial (National Clinical Trials identifier NCT00053898) and the second IBIS (IBIS-II) trial (DCIS),\(^{149}\) are currently ongoing. Although 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.150 In that trial, women received a single dose of trastuzumab or placebo 14 to 28 days before excisional surgery. No change in the size or growth rate of the excised HER2-positive DCIS was seen; however, immunologic responses were observed. The study was followed by a phase 3 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 2 trials have tested the anti-HER2 drug lapatinib, which inhibits both the epidermal growth factor receptor (EGFR) and HER2 tyrosine receptor kinases. Preclinical studies have demonstrated that lapatinib can prevent the development of HER2-positive breast tumors in mice.151 Decensi and coworkers conducted a pre-surgical phase 2 trial in women with invasive or noninvasive HER2-positive breast cancer testing the ability of lapatinib or placebo to suppress breast cancer cell growth.152 They showed that lapatinib was able to inhibit proliferation in both invasive and noninvasive breast cancers. A second pre-surgical phase 2 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 3 prevention trials.

**Prevention of TNBC.** Although antiestrogen 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 breast cancers (TNBCs). Preclinical and early clinical trials suggest several agents that may have the potential to prevent these cancers, including the cyclooxygenase-2 (COX-2) inhibitor celecoxib, retinoids, statins, epigallocatechin gallate (the active agent in green tea), and the antidiabetic drug metformin.153-163 Further clinical development of celecoxib and retinoids has been hindered by their associated toxicities.164-168 Metformin (850 mg twice a day vs placebo) is currently being tested in a phase 3 trial (NCT01101438) as adjuvant therapy for women with resected early stage breast cancer. Patients will be stratified according to hormone receptor and HER2 status, and the results may provide important information for the future development of metformin for the tertiary prevention of breast cancer, including TNBC. Phase 3 trials testing statins or epigallocatechin gallate in the prevention of any molecular subtype 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 3 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 because of 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 US Preventive Services Task Force currently recommends that clinicians engage in shared, informed decision making and offer to prescribe these medicines for women aged 35 years and older who are at an increased risk of the disease and at low risk of adverse medication effects.169 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.169 Recent data from a 2013 meta-analysis of all nine SERM trials146 and from extended follow-up of the IBIS-I trial147 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 5 years to prevent one breast cancer in the next 20 years.147 Whether such data will help to improve the 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.170 Yet cervical cancer remains a major cause of cancer-related death throughout the world, particularly in low and middle-income countries.171 Although cervical cancer screening remains critical for cervical cancer prevention in the United States and around the world, the human papillomavirus (HPV) vaccines offer an important molecular prevention option for cervical cancer as well as other anogenital cancers. The HPV vaccines represent the first vaccines to be marketed as cancer prevention vaccines.

**Vaccine trials.** The sexually transmitted HPV represents the leading sexually transmitted disease in the United States and is now known to be the predominant cause of cervical cancer.172-175 Seventy percent of cervical cancer diagnoses result from HPV type 16 (HPV-16) and...
HPV-18, 2 of the nine high-risk HPV subtypes, all of which are now deemed carcinogenic.\(^{172}\) HPV-16 and HPV-18 have also been shown to cause vaginal, vulvar, penile, oropharyngeal, and most anal cancers; whereas HPV-6 and HPV-11 cause 90% of genital warts.\(^{176}\)

The prophylactic HPV vaccine administered before 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 before their first sexual activity.\(^{177,178}\) Koutsky and colleagues analyzed the preventive effects of an HPV-16–specific vaccine versus placebo in 2392 women ages 16 to 23 years on the incidence of HPV-16 infection.\(^{33}\) That study showed HPV-16 incidence rates of 0 and 3.8 per 100 women in the HPV-16 vaccine and placebo groups, respectively (100% efficacy; 95% CI, 90-100).

After the success of the univalent HPV-16 vaccine, Koutsky and colleagues conducted the phase 3 Females United to Unilaterally Reduce Endo/Ectocervical Disease (Future II) clinical trial. That study tested the effectiveness of the quadrivalent HPV-6/HPV-11/HPV-16/HPV-18 vaccine Gardasil versus placebo in more than 12,000 women between ages of 16 and 26 years for the prevention of high-grade HPV-16/HPV-18–related cervical lesions.\(^{36}\) The study was terminated early because of 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, vs placebo). Furthermore, vaccination of women infected with one or more of the four HPV types targeted by Gardasil before 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.\(^{179-183}\) Bivalent vaccine safety has since been evaluated across 11 clinical trials,\(^{184}\) as well as in a meta-analysis of bivalent and other vaccines,\(^{185}\) which reported that the most common adverse events in the vaccine versus control groups included injection–site symptoms, fatigue, headache, and myalgia, and there was 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 individuals, the FDA approved Gardasil (MERCK) for the prevention of HPV-6, HPV-11, HPV-16, and HPV-18 in 2006 and Cervarix (GlaxoSmithKline) for the prevention of HPV-16 and HPV-18 in 2009 (Table 1). Recommendations for HPV vaccine use were subsequently released by the US Preventive Services Task Force,\(^{186}\) the American Society for Clinical Pathology, and the American Society for Colposcopy and Cervical Pathology.\(^{187}\) The American Cancer Society currently recommends that women be vaccinated for HPV at age 11 or 12 years and, with a physician’s recommendation, as early as 9 years or between ages 19 and 26 years.

Gardasil has also been shown to prevent HPV–related precancerous lesions, genital warts, and anal and penile cancers in men, and it may prevent head and neck cancer.\(^{188}\) This preventive efficacy for cancers among the male population has resulted in the recommendation of the Advisory Committee on Immunization Practices for the three-dose HPV vaccination series for males age 11 or 12 years, which may be initiated as early as 9 years of age, or for males ages 13 to 26 years upon physician consultation.\(^{177}\) However, the cost-effectiveness of vaccinating males is not as well-established as that for vaccinating females at the current recommended ages.\(^{189}\) 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.\(^{189}\)

In December 2014, the FDA approved the upgraded Gardasil 9 vaccine, which expands protection of the quadrivalent vaccine to five additional HPV strains (HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58) and can potentially prevent approximately 90% of cervical, vulvar, vaginal, and anal cancers.\(^{190}\) 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 it was equally effective as the quadrivalent vaccine in preventing the cancers and genital warts caused by the four HPV types shared between the vaccines.\(^{191}\)

**Chemoprevention-based studies.** Before 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 those 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 histologic 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 United States and in 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 for the treatment of high-grade dysplasia in patients with Barrett esophagus (BE) (Table 1). However, photodynamic therapy is being replaced by radiofrequency ablation with mucosal resection as the current endoscopic standard of care because of its improved efficacy and safety results. 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.

**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. The largest of these, conducted by Blot et al, examined 5 years (1986–1991) of treatment with four different vitamin and mineral combinations, at doses of one or two times the US-recommended daily allowances, in approximately 30,000 individuals. 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 = .06). A combination of selenium, β-carotene, and vitamin E supplements (which significantly decreased both gastric and total cancer deaths) resulted in a nonsignificant 4% reduction in ESCC deaths. After a 15-year follow-up, this same combination showed a significant 17% reduction in ESCC mortality in individuals younger than age 55 years but increased mortality in individuals aged 55 years and older. Limburg et al more recently tested the ability of 10 months of treatment with selenomethionine (200 μg daily) and celecoxib (200 mg twice daily) to improve mild or moderate squamous dysplasia (accepted histologic precursor to ESCC) in a 2 × 2 factorial RCT of 267 Linxian residents. Whereas celecoxib failed to exhibit any effect on either mild or moderate dysplasia, selenomethionine resulted in a significant improvement (P = .02) in mild dysplasia.

These trials suggest that vitamin or mineral supplements in nutritionally compromised populations at high risk for ESCC may have preventive potential. Nevertheless, because of 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. Several 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.

**EAC.** Only one phase 2B chemopreventive RCT has been conducted for EAC, although its incidence has increased by 463% and 335% among white males and females, respectively, in the United States between the periods 1975 to 1979 and 2000 to 2004. A lack of convincing EAC animal models has hindered the identification and development of chemopreventive agents for this disease. Heath et al compared celecoxib (200 mg twice daily for 48 weeks) versus placebo in 100 patients with BE (a neoplastic precursor to EAC). Their study results demonstrated no difference in dysplasia regression between study arms; however, quantitative endoscopic data suggested a reduction in the BE surface area in the celecoxib group after 1 year of treatment. The largest phase 3 EAC trial is the Aspirin Esomeprazole Chemoprevention Trial (AspECT), a large, multicenter trial testing the chemopreventive effect of the proton-pump inhibitor esomeprazole (20 or 80 mg twice daily) with or without aspirin (300 mg daily) in reducing either all-cause mortality or the conversion rate from Barrett metaplasia to adenocarcinoma or high-grade dysplasia. 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), NSAIDs have been and continue to be the focus of chemopreventive agent development for 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 CRC and possibly other cancers. 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. Large, population-based trials of alternate-day aspirin use from the Women’s Health Study (100 mg) and the Physician’s Health Study (325 mg) did not initially demonstrate significant effects of aspirin in the primary prevention of CRC after 10 and 5 years of treatment, respectively. Results from the Physician’s Health Study remained null after 12 years of follow-up. However, after an overall follow-up of 18 years, recent results from the Women’s Health Study indicate a significantly reduced risk for CRC in healthy women (HR, 0.80; 95% CI, 0.67–0.97; P = .021). 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 5 or more years and after a latency of 10 years. Three smaller trials in individuals with a prior history of adenomas demonstrated a 20% to 30% reduction in risk of recurrent adenomas after 1 to 3 years of follow-up. Risk reduction in each trial was generally greater for patients with advanced and/or large (>5 mm) adenomas. However, follow-up results of one of those trials did not confirm these initial findings,
citing no significant differences between the aspirin and placebo groups after 4 years of treatment.56 Another trial of individuals with previously resected, early stage CRC identified a significant 35% reduction in adenoma incidence after 3 years of treatment with aspirin (325 mg daily) given in an adjuvant context.24 The Colorectal Adenoma/Carcinoma Prevention Program 1 (CAPP-1) and CAPP-2 trials examined aspirin (600 mg daily) in individuals with the hereditary CRC syndromes of familial adenomatous polyposis (FAP) and Lynch syndrome, respectively.65,66 CAPP-1 identified a nonsignificant reduction (23%) in polyp count and a trend toward reduced largest polyp size within the aspirin-treated group after a median of 17 months of intervention.66 CAPP-2 found a significant reduction in the risk of CRC (59%) only in those who completed at least 2 years of intervention after a mean of 55.7 months of follow-up.65 The CAPP-3 trial will compare the effect of different doses of aspirin in Lynch syndrome.65

Although the dose and duration of aspirin differ among the trials, overall, data from RCTs support the use of aspirin to protect against CRC and are 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 1 to 3 years when endoscopies are performed on schedule as part of an RCT protocol.60 Additional trials are needed to determine the optimum dosing regimen and to answer remaining questions regarding which molecular subtypes of CRC might be prevented. Observational data have already suggested that the benefit of aspirin may depend on mutations in PIK3CA (phosphatidylinositol-4,5-biphosphate 3-kinase, catalytic subunit α) in individuals with a diagnosis of colon cancer; and familial data suggest that a mutation in SLCO2A1 (solute carrier organic anion transporter family, member 2A), a member of the prostaglandin catabolic pathway, is associated with early colonic neoplasia and NSAID resistance.207,208

In addition to aspirin, COX-2 inhibitors and sulindac have also demonstrated efficacy in RCTs. Celecoxib has been tested in 3 trials: a small trial of 77 FAP patients51 and the subsequent Adenoma Prevention with Celecoxib (APC)60 and Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP)59 trials of individuals with a history of adenomas. The FAP study demonstrated significant decreases in polyp number and overall polyp burden after 6 months of treatment with celecoxib (400 mg twice daily)51 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 patients with FAP was sacrificed because of challenges in conducting confirmatory trials in this high-risk setting. Subsequently, significant protective effects were also observed in the APC and PreSAP trials.59,60 However, both trials identified up to a 2-fold to 3-fold higher risk of serious cardiovascular events among those taking celecoxib.59,60 Later post hoc analyses of 6 publically funded trials suggested that this risk may be restricted to those with an elevated baseline risk of cardiovascular disease.209,210 Nevertheless, because CRC and cardiovascular disease share several risk factors and definitive data are lacking, celecoxib is not currently recommended for the prevention of CRC.

Sulindac has demonstrated mixed results in 4 small trials (range, 10-44 individuals) involving patients with FAP. A primary prevention trial testing the ability of 4 years of sulindac treatment to prevent adenoma development or to reduce the number and/or size of adenomas in phenotypically unaffected carriers of the FAP genotype failed to demonstrate an effect.52 However, results from secondary prevention trials have been largely positive, with 3 trials demonstrating a protective effect of sulindac on the number, size, and regression of adenomas.46-48 A fourth trial in individuals with sporadic adenomas did not demonstrate a significant effect on adenoma regression after 4 months of treatment.211

The harms associated with the long-term use of NSAIDs are well established and include gastrointestinal (GI) and cardiovascular toxicities. A recent meta-analysis of 280 trials of NSAIDs versus placebo and 474 trials of one NSAID versus another demonstrated that all NSAID regimens increased upper GI complications and that coxibs and diclofenac significantly increase vascular events, primarily major coronary events, as well as vascular death.212 However, that meta-analysis also showed that these risks can be predicted once the baseline risks for such hazards are known, which could allow for tailoring the use of these medicines and, as the authors state, aid in clinical decision making.212 Although rare, another potential side effect of prolonged NSAID use is diaphragm disease, which is characterized by short, circumferential lesions most commonly located in the small intestine that cause luminal stenoses.213,214 In a study using capsule enteroscopy, 2% of those receiving traditional NSAIDs showed evidence of strictures in the small bowel, whereas those receiving COX-2 inhibitors did not exhibit such strictures.215 Overall, 1% of all patients who were taking NSAIDs had strictures.215 Notably, such strictures have also been observed in patients for whom NSAID use could not be proven.213 It has been suggested that the formation of diaphragms may be a nonspecific response to various insults to the intestine.213 In 2007, the US Preventive Services Task Force recommended against the use of aspirin and NSAIDs to prevent CRC in those at average risk of the disease, because the Task Force concluded that, overall, there was good
evidence of at least moderate harms associated with their use. 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 (3 grams daily [1200 mg elemental calcium]) given over 4 years to individuals with recently resected adenomas demonstrated a 19% reduction in recurrent adenomas. However, in a recent and larger RCT of both calcium and vitamin D over 3 to 5 years, Baron et al observed that these agents were ineffective in reducing the risk of colorectal adenomas.

Colorectal chemoprevention has also provided a forward-looking opportunity to test agent combinations, which are widely anticipated to be more effective in prevention, based on exciting preclinical data and the dominant role of therapeutic combinations in cancer treatment. Sulindac was tested in combination with DFMO in 375 individuals with sporadic adenomas. Combined sulindac-DFMO treatment proved successful, resulting in a remarkable 70% reduction in recurrent adenomas versus placebo, with no significant differences in adverse effects. 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 patients with previously resected CRC (NCT01349881), a trial of DFMO in conjunction with aspirin (NCT00983580) in individuals with current or previous adenomas, and trials of DFMO and celecoxib (NCT0033371) and sulindac and erlotinib (NCT01187901) in patients with FAP.

In addition to those with FAP and Lynch syndrome, individuals with inflammatory bowel disease (IBD), either ulcerative colitis (UC) or Crohn disease, also have an increased risk of colon cancer compared with the general population, although estimates vary regarding the magnitude of this risk. 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 have been tested in phase 3 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 that it reduces the incidence of CRC in this context, although other studies have suggested no effect. Three meta-analyses have been conducted on the topic, including two that reported significant protective effects of 5-ASA on CRC or colorectal neoplasia in UC and one that reported a significant protective effect in clinic-based populations but not in nonreferral populations. Conducting an RCT of 5-ASA is challenged by the finding 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. Aside from 5-ASA, ursodeoxycholic acid (UDCA) also shows some promise in this area. A few early observational studies and 2 recent meta-analyses have suggested that UDCA may prevent CRC in patients with IBD, particularly in those who also have primary sclerosing cholangitis. However, some data suggest that high doses of UDCA may actually increase the risk of CRC in patients with primary sclerosing cholangitis. 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 nonmuscle-invasive bladder cancer (NMIBC), which are considered precancerous in most other organs. 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) for 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 6 weekly instillations of intravesical BCG use in 9 patients with recurrent bladder cancer. After that trial, small RCTs by Lamm et al and Pinksy et al demonstrated that BCG reduced tumor recurrence. An RCT by Herr et al of 86 patients with superficial bladder cancer demonstrated that intravesical BCG with TUR could significantly delay disease progression and increase overall survival compared with TUR alone. Ten-year follow up data from that RCT confirmed those findings, with a 10-year disease-specific survival rate of 75% compared with 55% in those who received TUR alone. Several RCTs have examined the clinical benefit and optimal regimen of maintenance therapy compared with induction therapy alone. However, because of the small size of many of those studies, the results are difficult to interpret. The largest study by Lamm et al of 384 patients demonstrated that patients who received 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).
That study served 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.228

Valrubicin offers a second line of treatment for patients with BCG-refractory carcinoma in situ 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, noncomparative study of 90 patients with carcinoma in situ who failed at least two courses of intravesical therapy, at least one of which was BCG. The findings demonstrated that six weekly instillations of valrubicin 800 mg were well tolerated, 21% of patients remained disease-free 6 months after treatment, and responses were durable, with a median response time greater than 18 months.88 Those 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 3 trial data along with data from a supportive phase II/III trial (the A9303 trial). Based on the updates to the data originally reported in Steinberg et al,88 the complete response rate changed from 21% to 18%, which is identical to the complete response rate reported in the supportive A9303 trial by Dinney et al.89 The supportive trial also demonstrated a disease-free status of 22% at 6 months, 10% at 1 year, and 4% at 2 years.89 Because patients in the A9303 trial were less highly treated than patients in the previous phase 3 trial, Dinney et al concluded that valrubicin was both safe and efficacious in highly pretreated populations as well as those with few previous therapies.89 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 nonmelanoma skin cancers (NMSCs). Importantly, two specific skin cancers, cutaneous squamous cell carcinoma (cSCC) and melanoma, have strong clinicopathologic evidence for developmental sequences that proceed throughpreneoplastic intermediates, thus enabling targeting the treatment of specific preneoplastic lesions for cancer prevention.

Actinic keratoses and cSCC. cSCC comprises 15% to 20% of skin cancers, numbering over 700,000 per year in the United States.229,230 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 (AK), to invasive carcinoma. AKs are the most common precancerous lesion in humans,231 affecting upward of 5.5% of women and 13.9% of men in the United States and accounting for 5.2 million visits per year and an estimated annual cost of $920 million.232 Approximately 65% to 72% of cSCCs arise in association with preneoplastic AKs,233 indicating that interrupting progression at this stage would be a clinically important intervention.

In accordance with this, several modalities are frequently used for treating AKs. Many are purely destructive, such as electrodesiccation, curettage, cryosurgery, or chemical peels.234 Five active topical agents are currently FDA-approved for the treatment of AKs: 5-fluorouracil cream, diclofenac gel, imiquimod cream, ingenol mebutate gel, and δ-aminolevulinic acid photodynamic therapy (Table 1) (masoprocol was withdrawn from the US 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.235 Overall, their individual efficacy in clearing AKs is comparable, with differences in adverse effects and cosmesis.235 None of these agents have been studied in a phase 3 randomized trial to prove efficacy in the prevention of NMSC as a primary endpoint, because it has been assumed that any expected benefit in AKs would result in a reduction in cSCC/basal cell carcinoma (BCC) incidence, and changes in AKs have been interpreted as a sufficient clinical benefit.235

Retinoids represent the most commonly tested agents 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.99 This benefit was not observed in a recent trial of acitretin in nontransplantation patients.106 Similarly, a recent trial of topical tretinoin cream involving 1191 veterans showed no benefit in lowering AK, BCC, or cSCC incidence, with a greater number of skin-related adverse events.105 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.236 Another potential disadvantage of retinoids is that discontinuation is associated with a rebound effect and quick loss of the preventive effect.236

There is abundant preclinical evidence for cancer chemopreventive efficacy of COX-2 inhibition in skin and GI tract; and, although a large phase 3 trial demonstrated no benefit in reducing AK incidence during and after 9 months of celecoxib (200 mg daily), there were significant reductions in the incidence of both BCC (relative risk, 0.40; 95% CI, 0.18-0.93; P = .032) and cSCC (relative risk, 0.42; 95% CI, 0.19-
0.93; P = .032). 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. 238 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 transplantation recipients in a small trial, 239 suggesting that further study is warranted.

Recently, the ornithine decarboxylase inhibitor DFMO has shown efficacy in reducing BCC incidence (0.40 events/patient-years vs 0.28 events/patient-years; P = .03) in individuals with a prior history of NMSC, although no significant effects were noted on overall NMSC or cSCC incidence. 104 That trial was distinguished by its long period of intervention (4–5 years) and the simultaneous demonstration that the target, ornithine decarboxylase, was inhibited in vivo, although it could not be established as a surrogate endpoint. Importantly, long-term follow up for the 5-year period after drug withdrawal was conducted, showing that the trend in lower NMSC rates persisted, although the difference was statistically insignificant. 240 The recent approval of the systemic hedgehog pathway inhibitor vismodegib has revolutionized the treatment of advanced and metastatic BCC. 108,241 A randomized phase 2 trial examined both the efficacy of treatment for and suppression of new BCCs in patients with basal cell nevus syndrome, who develop hundreds of BCCs as a result of loss-of-function mutations in the patched 1 gene (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 < .001), demonstrating a strong chemopreventive effect of this drug in this high-risk setting. 108

Melanoma. Melanoma is the third most common form of skin cancer, accounting for over 76,000 cancer diagnoses and 9000 deaths per year in the United States. 242 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. 243,244 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. 245

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 (eg, statins and fibrates) and lower melanoma incidence 246; however, early phase trials with lovastatin have failed to substantiate effects on melanoma or dysplastic nevi incidence or pathobiology. 247 There are conflicting epidemiological data on whether there is a protective effect of NSAID use on melanoma risk. 245,246 The Women’s Health Study, which used 100 mg of aspirin every other day, demonstrated no effect on melanoma risk, although that dose may have been too low. 57 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 proapoptotic metabolite of sulindac, were achieved in benign nevi after 8 weeks of oral sulindac (150 mg twice daily), but this did not result in significant modulation of vascular endothelial growth factor A 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 remains to be established. 248

Currently, there are a few clinical melanoma prevention trials testing systemic sulindac, sulforaphane, vitamin D3, lovastatin, and N-acetylcysteine (clinicaltrials.gov). 246 Of these, there are two ongoing phase 3 adjuvant studies of vitamin D3 supplementation, one in resected stage II melanoma patients with primary endpoints of disease-free and overall survival after 3 years of treatment and 2 years of follow-up (NCT01264874) and the other in patients after resection of their first cutaneous melanoma with a primary endpoint of disease-free survival during 3.5 years of follow-up after 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 groups have been limited to small trials, all of which have demonstrated efficacy. Systemic acitretin in renal transplantation recipients significantly lowered cSCC and AK incidences, 99 and topical T4N5 endonuclease reduced annual AK incidence (treatment vs placebo, 8.2 vs 25.9) and BCC incidence (treatment vs placebo, 3.8 vs 5.4) in patients with xeroderma pigmentosum who lacked nucleotide excision repair. 96 The phase 3 trial experience with vismodegib, performed in patients with an inherited predisposition to BCC, 108 emphasizes that agents useful for therapy may also be useful for chemoprevention. One major issue is that appropriate molecular surrogate endpoints reflecting 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 (eg, other squamous cell carcinoma types). Ideally, the confluence of compelling preclinical data; appropriate risk cohorts, as suggested by the success of trials in high-risk groups; 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 3 Trials But No Approved Agents

Head and neck

Multiple agents for oral cancer chemoprevention have been investigated over the past 3 decades, and retinoids are the most extensively studied drugs in this setting. Unfortunately, these intensive investigations failed to develop a standard pharmacologic approach to prevent cancers in patients with oral premalignant lesions (OPLs) because of either drug toxicity 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, RNA expression signatures, EGFR overexpression/copy number gain, and loss of heterozygosity (LOH) profiles.

Currently, LOH represents the most robust marker of cancer risk in OPLs. Building on this finding, the first personalized medicine cancer prevention trial based on molecular risk markers was completed: the Erlotinib Prevention of Oral Cancer (EPOC) study. In that 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 (ie, LOH-positive) 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-negative). Low-risk patients were routinely followed in clinic without active intervention. High-risk patients (N = 150) received oral erlotinib (150 mg daily) or placebo for 12 months and participated in follow-up for ≥24 months. The primary trial results reported at the 2014 American Society for Clinical Oncology Annual Meeting failed to demonstrate improved cancer-free survival with erlotinib over placebo (the primary endpoint). There was a nonsignificant trend of benefit from erlotinib on cancer risk during the 12-month treatment period, which did not persist posttreatment. The most significant secondary finding was that patients in the EPOC trial who developed an erlotinib-related rash (grade ≥2) exhibited significantly increased cancer-free survival. Although 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 cancer and head and neck cancer therapeutic trials. Nonetheless, it has been demonstrated that LOH is a promising biomarker of cancer risk in patients with premalignant conditions (including Barrett esophagus) that can be used to 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 oropharyngeal squamous cell carcinoma (OPSCC) is principally caused by 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 it is expected to exceed the yearly number of cervical cancers by the year 2020. Among men and women ages 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 HPV-16 infection; and, once this behavior was adjusted for, age cohort and race were no longer associated with oral HPV-16 infection. Although clear vaccine efficacy against oral HPV infections is not known, in a recent secondary analysis of a trial investigating vaccine efficacy of the bivalent HPV-16/HPV-18 vaccine against cervical infections and lesions, Herrero et al found that oral HPV prevalence 4 years after vaccination was significantly lower in the vaccine arm versus the control arm. These results are promising for the prevention of both oral HPV infection and OPSCC.

Hong and colleagues reported that 1 year of high-dose 13-cis-retinoic acid (13-cRA) significantly reduced the incidence of second primary tumors (SPTs) in patients with curatively treated stage I through IV head and neck squamous cell carcinoma. However, a subsequent large-scale National Cancer Institute Intergroup phase 3 trial of low-dose 13-cRA involving 1190 randomized patients with stage I and II head and neck squamous cell carcinoma reported no difference in SPTs and/or recurrence rates between the 13-cRA and placebo arms. To determine whether genetic background influences the risk of SPT/recurrence and whether genetic markers could be used to predict which patients are 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. The most significant findings were for the common genotype nuclear retinoid X receptor (RXRA): rs3118570 SNP located within an intron of the gene...
encoding 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 who thus were good candidates for intervention.269 In addition to its prognostic value, RXRA:rs3118570 was predictive of 13-cRA efficacy, identifying this receptor as a target for chemoprevention with strong biologic plausibility.269 Although 13-cRA was once among the most promising agents for cancer chemoprevention, outcomes of phase 3 trials were disappointing.110,112 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 cancer270 and the remarkable recent progress in identifying multiple targetable molecular driver mutations associated with lung carcinogenesis,271 there are as yet no FDA-approved interventions to prevent lung cancer. The concept of prevention remains highly appealing, because 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.272 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.273,274 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 the identification of multiple potential driver mutations raising the possibility that different preventive interventions or combinations may be necessary for different molecular subtypes of lung cancer, as with breast cancer.271

Evidence-based clinical practice guidelines regarding chemoprevention of lung cancer have recently been published.275 As summarized in Table 3, phase 3 chemoprevention trials specifically designed to assess effects on lung cancer development have all shown either no efficacy or harm. Those trials focused primarily on vitamins and micronutrients, based largely on epidemiologic evidence (as in the case of β-carotene) or secondary endpoints from clinical trials (as in the case of selenium) and a general perception of the safety of dietary supplements.116,118,121 The individual studies will not be discussed here. Instead, we will focus on the important lessons from these large trials.

The α-Tocopherol, β-Carotene (ATBC) Study and the β-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 β-carotene and/or α-tocopherol versus placebo (ATBC) or β-carotene and retinol versus placebo (CARET).116,118 Contrary to expectations, the risk of lung cancer was increased by 16% and 28%, respectively, in current smokers but not former smokers. Consistent with the hypothesis of a negative interaction between β-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 β-carotene and/or aspirin or placebo.117 The β-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 β-carotene actions.276 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.277 Thus, the β-carotene experience emphasized the need for assessing multiple types of evidence when selecting a specific intervention strategy for phase 3 trials, even if this requires additional work to be done before trial launch.

The Eastern Cooperative Oncology Group 5597 trial of selenium supplementation in patients with resected stage I nonsmall 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.121 That 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,274 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.278 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 3 trials have served to energize the development of phase 2 preliminary efficacy
trials that strive to add participant-level information on efficacy to the mechanistic, preclinical, and epidemiologic data that must be considered before launching phase 3 trials. Multiple studies examining the effects of interventions on lung cancer precursor lesions, such as bronchial dysplasia and computed tomography (CT)-detected indeterminate lung nodules, or putative intermediate endpoints, such as the proliferation index, have been reported or are under way, as discussed below.275 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.279 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 CRC and esophageal cancers. The prevention of multiple chronic diseases with a drug that is cheap and whose side effect profile is well understood is very appealing. Several phase 2 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 the identification of promising agents is the development of new clinical trial 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 2 trials.280 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 pathway, which is frequently mutated in squamous cell carcinomas arising from tobacco-damaged epithelia281 and appears to be activated early (at the dysplasia stage) during lung carcinogenesis.282 Reversion of this activation signature by the agent myo-inositol, corresponding to regression of dysplasia, in a small phase 1 trial282 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,283 these novel approaches and new agents offer hope that disseminated lung cancer indeed can be prevented.

Prostate

The Prostate Cancer Prevention Trial (PCPT) tested finasteride (5 mg daily), an inhibitor of type II 5α-reductase that converts testosterone to the more potent androgen dihydrotestosterone, for 7 years (vs placebo). PCPT randomized 18,882 men aged 55 years and older who had normal digital rectal examinations and prostate-specific antigen levels. 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.122 Consequently, despite the finding that PCPT met its primary prostate cancer efficacy endpoint, the FDA did not approve finasteride use for the prevention of prostate cancer.284 That trial and its subsequent FDA decision have generated much debate and follow-on analyses of the high-grade finding, including an extensive pathologic study285 and complex statistical modeling.286 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 (eg, finasteride-driven artifact vs new finasteride-induced high-grade cancers) and found no significant between-group differences in the rates of overall survival or survival after the diagnosis of prostate cancer.287 However, the 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.287

The REDUCE trial (Reduction by Dutasteride of Prostate Cancer Events) tested the efficacy of another 5-α reductase inhibitor, dutasteride (0.5 mg daily), in preventing prostate cancer among men with an elevated prostate-specific antigen level (2.5-10 ng/mL) and a negative prostate biopsy. It demonstrated that the men who received dutasteride had a 23% overall reduction in the diagnosis of biopsy-detected prostate cancer compared with placebo.124 This reduction was because of a decreased incidence of lower grade prostate cancer (Gleason score, ≤6). Unfortunately, as with finasteride, dutasteride was associated with increased risk of high-grade prostate cancer (Gleason score, 8-10).

In 2001, the US National Cancer Institute initiated the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which tested whether selenium (200 μg daily from L-selenomethionine), or vitamin E (400 IU daily of all-rac α-tocopheryl acetate), or both could reduce prostate cancer risk in over 35,000 men. Study supplementation stopped 3 years before the expected trial end date, because interim analyses showed a very low likelihood of benefit
with continued intervention. At that time, the results demonstrated that vitamin E alone modestly increased prostate cancer risk (HR, 1.13; \( P < .06 \)). Unfortunately, this increased risk of prostate cancer became statistically significant with additional follow-up (HR, 1.17; \( P < .008 \)).

A recent follow-on analysis of SELECT investigated whether selenium or vitamin E might benefit men with low baseline selenium. Contrary to this hypothesis, vitamin E supplementation (alone) increased risk of total prostate cancer by 63% \( (P = .02) \) in men with low baseline toenail selenium (<40th percentile), and this effect was stronger for high-grade (111%; \( P = .01 \)) versus low-grade (46%; \( P = .09 \)) cancer. Among men with high baseline toenail selenium (≥60th percentile), selenium supplementation increased the risk of high-grade cancer by 91% \( (P = .007) \). 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 selenium, 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.

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

Cancers With Probable Risk-Reduction Strategies Based on Treatment/Prevention of Infectious Agents

Liver/hepatocellular

Hepatitis B virus (HBV) and hepatitis C virus (HCV) 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 and HCC incidence rates in endemic regions (eg, Taiwan). Perhaps most importantly, 30-year outcomes of the Taiwanese vaccination program reveal a 90% reduction in the mortality rate ratio of HCC between the periods 1977 to 1980 and 2001 to 2004, demonstrating that prophylaxis against HBV infection prevents HCC. While a vaccine for hepatitis C is expected to have similar preventive effects for HCC, aspects unique to HCV challenge vaccine development. Nevertheless, advances have been made in this area, and various vaccination strategies are currently being explored.

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 who were born between 1945 and 1965. For the treatment of viral hepatitis and downstream HCC prevention, antiviral therapy (eg, interferon and various nucleoside analogs, including ribavirin, lamivudine) may slow or block the progression of chronic liver disease. A recent compilation of antiviral treatment trials identified five RCTs reporting on HCC incidence. Two trials evaluated interferon-2a, one evaluated interferon-2b, and two evaluated lamivudine. The pooled relative risk from these five trials suggests a nonstatistically significant 43% reduction in HCC risk after antiviral treatment. Multiple antiviral HCV regimens are available, but RCT data examining the preventive efficacy of antivirals on HCC incidence per se are currently lacking. However, observational data from 12 different studies totaling nearly 26,000 individuals suggest that a sustained virologic response after antiviral therapy is associated with reduced HCC risk. While increased understanding of the effect of antivirals 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 (noncardia)

The gram-negative, microaerophilic bacterium Helicobacter pylori \((H. pylori)\) is associated with the majority of noncardia gastric cancers (GCs) worldwide. 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 the eradication of \(H. pylori\) as a strategy to prevent noncardia GCs is emerging. Several RCTs of various triple therapies have been conducted in individuals from regions with high rates of GC incidence. However, results from those trials are conflicting and often nonsignificant. 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. This is the first study to demonstrate such a finding, and it is possibly because of the long-term follow-up in that study. A recent analysis of trial data by subgroup suggests that treatment benefits extend to older individuals, those with advanced baseline histopathology, and those with posttreatment infection. Although 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 GC 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 GC.308

In addition to *H. pylori* eradication with triple therapy, antioxidants and NSAIDs have also been tested for a chemopreventive benefit in RCTs. Trials of antioxidant supplements are based on the finding that diets high in fresh fruits and vegetables have been associated with a reduced risk of GC. Vitamins C and E, selenium, β-carotene, and various combinations thereof have been tested in several trials, including some of the previously mentioned trials examining *H. pylori* eradication.39,40,125,127 Results of these trials are conflicting and difficult to interpret. Consequently, data do not currently support the chemopreventive benefit of antioxidants in GC.

Regarding NSAIDs, there are some preclinical data to suggest that aspirin and other nonsteroidal anti-inflammatory agents 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 1024 *H. pylori*-infected patients with advanced gastric lesions to anti-*H. pylori* treatment for 7 days, celecoxib for 24 months, both, or neither.129 Their 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.129 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 that reported deaths from various cancers.279 Those results showed a significant protective effect (HR, 0.42; 95% CI, 0.23–0.79) of aspirin on GC mortality for patients who received treatment for more than 10 years.279

In summary, there is emerging evidence that eradication of *H. pylori* with triple therapy may prevent noncardia GC and that NSAIDs may offer a true chemopreventive strategy for GC. Additional high-quality phase 3 trials are required of each potential strategy to confirm the suggested protective effects. Two phase 3 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 combined lansoprazole, amoxicillin, clarithromycin triple therapy to reduce the risk of GC in first-degree family members of patients who have GC.

The role of *H. pylori* in cardia GCs is unclear. Results of observational studies are mixed, with those in Asian populations generally suggesting that *H. pylori* increases the risk of cardia cancer309 and those in Western populations suggesting a protective or null association.310–312 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 in those countries and an over representation of misclassified gastroesophageal reflux disease-associated lower esophageal malignancies.309 A 2011 meta-analysis of 34 studies suggested no overall association between *H. pylori* and gastric cardia cancer but an increased risk in high-risk (ie, Asian) settings and a suggestive inverse association in low-risk (ie, Western populations) settings.313 The authors suggest that these results support the hypothesis of a mixed distribution of etiologically distinct types of cardia cancer, in which one type occurs through *H. pylori*-associated gastric atrophy, and the other occurs in nonatrophic gastric mucosa and is driven by damage from acid/bile in the distal esophagus, similar to esophageal adenocarcinoma.313 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 or cancer has been challenged by some,314 recent genomic data highlighting the extreme genetic complexity found in advanced cancers question a continued emphasis on the development of later stage therapies versus strategies targeting earlier stages of carcinogenesis. Nevertheless, order for chemoprevention to be fully realized as an effective strategy, several 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 precancer 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 in which 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 (eg, triterpenoids) and strategies involving intermittent dosing and/or drug combinations should be a high priority for testing in clinical trials.62,315,316 Recent experience with preventive combinations offer great hope,62 and some studies suggest that some agents used in cancer treatment (eg, 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 because of inherited germline mutations (eg, BRCA carriers) or specific exposure histories (eg, former smokers), offer several advantages over average-risk cohorts, including more power over shorter time frames and reduced cost. Smaller, cheaper, and faster trials will facilitate accelerated
the development of promising chemopreventive agents. Finally, integrative risk assessment and long-term outcome determinations across multiple diseases (eg, 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, 16 years) data from the IBIS-I trial, which showed a greatly improved benefit-to-harm ratio for tamoxifen.\(^\text{147}\) One can only imagine the complexity and relevance of such a consideration applied to an agent like aspirin, which reduces the risk of cardiovascular disease events and seems to reduce the risk of GC, esophageal cancer, and CRC, but increases the risk of bleeding and upper GI ulcers. Yet this is the dilemma facing physicians daily. As chemoprevention evolves, the optional approach to cancer is likely to transition from one based solely on treatment to one based on prevention, including lifestyle modifications, risk-reducing pharmacologic agents, and early detection, as neatly illustrated in the evolving management of cardiovascular disease over the last 2 to 3 decades.

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