CHAPTER 4 Medical Approaches to Cancer Prevention

Barbara K. Dunn, MD, PhD • Peter Greenwald, MD, DrPH

KEY POINTS

- Medical intervention to prevent cancer is generally targeted to individuals at increased risk of one of the common adult epithelial tumors (breast, prostate, lung, colon, skin).
- Cancer preventive agents have been U.S. FDA-approved for breast cancer (i.e., tamoxifen and raloxifene) and certain topical agents for skin cancer.
- Third generation aromatase inhibitors, such as exemestane and anastrozole, have shown promise in the prevention of ER-positive breast cancer: Exemestane is farther along, having been shown to decrease breast cancer risk in a primary breast cancer prevention trial.
- Aspirin may be appropriate as an anticancer agent for those at a high risk of colon cancer, although the potential for gastrointestinal bleeding should be closely monitored.
- Special attention to potential toxicities should be made when prescribing agents for cancer prevention in otherwise healthy individuals.

APPROVED AND PHASE III-TESTED CHEMOPREVENTIVE AGENTS

Only a few agents have been shown to decrease the risk of common cancers, mainly the hormonally responsive tumors (breast and prostate cancer), in high-risk individuals (see Table 4-1).1–13

Breast Cancer

The first chemopreventive agent to be approved by the U.S. Food and Drug Administration (FDA) for a cancer prevention/risk reduction indication for a given cancer was tamoxifen, a selective estrogen receptor modulator (SERM) that has been widely used to treat women who already had breast cancer. In four independent tamoxifen-versus-placebo prevention trials, tamoxifen reduced breast cancer by 38% overall and estrogen receptor (ER)–positive breast cancer by 48%.4 Concerns remain, however, about the rare tamoxifen toxicities of endometrial cancers and venous thromboemboli, both primarily in postmenopausal women. The osteoporosis SERM raloxifene subsequently received U.S. FDA approval for breast cancer risk reduction when the Study of Tamoxifen and Raloxifene (STAR) trial showed that raloxifene had about equal efficacy to tamoxifen in reducing first primary cancers and did not cause endometrial cancer, making it a less toxic alternative.6–8 Despite strong clinical trial evidence, U.S. FDA approval, and endorsement by respected professional organizations,6,14–16 the acceptability of preventive tamoxifen and raloxifene to high-risk women and their PCCs has been limited.17,18 Several reasons for this reluctance include toxicities (especially tamoxifen), the number needed to be treated (NNT) to see benefits (Fig. 4-1),18,19 the lack of easily measurable surrogates (comparable to the cardiovascular [CV] biomarkers, blood pressure, or cholesterol levels) for invasive cancer risk, and the restrictive list of attributes that make a woman a good candidate for preventive therapy (premenopausal status; very high risk because of atypical ductal hyperplasia [ADH], lobular carcinoma in situ [LCIS], or ductal carcinoma in situ [DCIS]; not at risk if/no history of thromboembolic disease; hysterectomy if postmenopausal).20 An interactive breast cancer risk...
<table>
<thead>
<tr>
<th>Preventive Agent</th>
<th>Prevention Trial or Epidemiologic Evidence Supporting Cancer Prevention Use (n) (eligibility)</th>
<th>Efficacy Data Experimental Agent versus Comparator</th>
<th>Side Effects Data</th>
<th>U.S. FDA Approval for Cancer Prevention Indication; or Strength of the Evidence and Recommendation for Risk Reduction</th>
<th>Recommendations Available to Primary Health Care Provider for Use in Cancer Prevention in Patients with the Following Characteristics</th>
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<tr>
<td>Tamoxifen (TAM)</td>
<td>NSABP P-1: BCPT (13,388) (≥60 y, 5-yr BC risk ≥1.66% per Gail model or LCIS)(^1)(^2), also IBIS-1(^3); Overview: 4 TAM prevention trials(^4)</td>
<td>BCPT: Invasive BC incidence: RR = 0.57 (95% CI, 0.46–0.70; (p &lt; .001)) Overview: RR = 0.62; 38% reduction (95% CI, 28%–46%; (p &lt; .001))</td>
<td>Endometrial cancer (postmenopausal women); thromboembolic disease</td>
<td>U.S. FDA approved; strong phase III clinical trial</td>
<td>Premenopausal: 5-yr BC risk ≥1.66% per NCI BC RAT, LCIS-TAM is the only approved option(^5)(^6), Postmenopausal: 5-yr BC risk ≥1.66% per NCI BC RAT(^5)(^6), or LCIS; Caution: H/O DVT, PE, stroke, TIA; endometrial cancer(^6)</td>
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<td>NSABP P-2: STAR (19,747) (postmenopausal, 5-yr BC risk ≥1.66% per Gail model or LCIS)(^7)(^8)</td>
<td>Invasive BC incidence (RAL versus TAM): Initial analysis: RR = 1.0 (95% CI, 0.82–1.28; (p = .83))^7; Updated analysis: RR = 1.24 (95% CI, 1.05–1.47; (p = .01))^8</td>
<td>Thromboembolic disease</td>
<td>U.S. FDA approved; strong phase II clinical trial</td>
<td>Postmenopausal: 5-yr BC risk ≥1.66% per NCI BC RAT(^7)(^8) or LCIS; Caution: H/O DVT, PE, stroke, TIA(^6)</td>
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<td>Exemestane</td>
<td>MAP.3: (4,560) (postmenopausal, 5-yr BC risk ≥1.66% per Gail model, 60 y; ADH, LH, LCIS, DGS S/P total mastectomy)(^9)</td>
<td>Invasive BC: HR = 0.35 (95% CI, 0.18–0.70; (p = .002))</td>
<td>Osteoporosis, arthritis, arthralgia, myalgia, diarrhea, nausea, hot flashes</td>
<td>Not approved for prevention; strong phase III clinical trial data recently published</td>
<td>Do not recommend outside clinical trials(^6); given recent positive outcome in MAP.3 for postmenopausal women at increased risk, may discuss with patient, although at present time there is no U.S. FDA label indication for BC prevention; Caution: H/O osteoporosis, osteopenia, arthritis (bone), musculoskeletal side effects</td>
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<td>Finasteride (FIN)</td>
<td>SWOG: PCPT (18,882) (normal risk, 55 y, PSA ≤3.0 ng/mL, DRE normal)(^10)</td>
<td>PC incidence: 24.8% (95% CI, 18.6%–30.6%; (p &lt; .001)) in 7-yr prevalence (13.4% FIN versus 24.4% Plac diagnosed with PD)</td>
<td>High-grade tumors (Gleason score 7–10); 37% of FIN versus 22.2% of Plac tumors; (RP_{	ext{radiated,tissue}} = 1.67) (95% CI, 1.44–1.93; (p &lt; .001)); (RP_{	ext{radial,male sex}} = 1.27) (95% CI, 1.07–1.50; (p = .009)); Sexual function/endocrine effects ((p &lt; .001), favors Plac): reduced ejaculate volume, erectile dysfunction, loss of libido, gynecomastia; Genitourinary ((p &lt; .001), favors FIN): BPH, urinary urgency, frequency, retention; TURP, prostatitis, UTI</td>
<td>U.S. FDA did not approve FIN for prevention based on toxicity data: increased risk of high-grade tumors; also added warning to package insert for BPH and male pattern baldness indications(^11); merits discussion with patient but caution regarding high-grade tumors(^12)</td>
<td>Not recommended for PC risk reduction</td>
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(continued)
### TABLE 4-1  Medical Interventions Recommended or Considered for Prevention of Common Adult Cancers (cont.)

<table>
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<tr>
<th>Preventive Agent</th>
<th>Prevention Trial or Epidemiologic Evidence Supporting Cancer Prevention Use (n) (eligibility)</th>
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<td>Dutasteride (DUT)</td>
<td>REDUCE (8,231/6,729 biopsied) (increased risk: 50–75 y, elevated PSA [2.5–10.0 ng/mL (50–60 y) or 3.0–10.0 ng/mL (&gt;60 y)]; or H/O single prostate biopsy within 6 mo)</td>
<td>PC incidence: 22.8% reduction (95% CI: 15.2%–29.8%; p &lt; .001) in 4-yr period (19.9% DUT versus 25.1% Plac diagnosed with PC)</td>
<td>High-grade tumors (Gleason score 7): 6.7% of DUT versus 6.8% of Plac tumors (p = .81); Tumors (Gleason score 6, 9, 10): 0.9% of DUT versus 0.6% of Plac tumors (p = .15); Tumors (Gleason score 6, 9, 10) in years 3 and 4: 0.5% (n = 12) of DUT versus &lt;0.1% (n = 1) of Plac (p = .003)</td>
<td>Not approved (toxicity—increased risk of high-grade tumors similar to FIN; also added warning to package insert for BPH and male pattern baldness indications)</td>
<td>Not recommended for PC risk reduction</td>
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<tr>
<td>Cancer Type: Colorectal Cancer</td>
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<td>Aspirin</td>
<td>Meta-analysis of 8 RCTs for primary and secondary prevention of CVD in high-risk patients</td>
<td>All cancers: HR = 0.66 (0.50–0.87; p = .003); GI cancers: HR = 0.46 (0.27–0.77; p = .003) (benefit seen only after 5 yrs)</td>
<td>GI and genitourinary bleeding</td>
<td>In widespread use; formal U.S. FDA approval is unlikely</td>
<td>Discuss with patient and tailor to individual risk (mainly GI bleeding): benefit profile; patients with increased risk of CVD may benefit most; USPSTF recommends against routine use of aspirin to prevent CRC in average-risk patients</td>
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<td>Sulindac + DFMO</td>
<td>Phase II RCT (375) (H/O adenomas): Sulindac 150 mg + DFMO 500 mg each day</td>
<td>Sulindac 150 mg + DFMO 500 mg versus Plac × 36 mo: reduced adenomas 70%, advanced adenomas 91.5%</td>
<td>No serious differences between arms of trial</td>
<td>Currently in phase II RCT: Plac versus sulindac versus DFMO versus sulindac + DFMO</td>
<td>Sulindac + DFMO combination not recommended for cancer prevention outside of clinical trial</td>
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<td>Celecoxib</td>
<td>Small (77) RCT (FAP-increased risk of CRC)</td>
<td>Celecoxib decreased polyp number by 28% at 6 mo versus Plac</td>
<td>Cardiovascular disease</td>
<td>1999 U.S. FDA approved for polyp number reduction in FAP; 2011 Pfizer pulled FAP indication</td>
<td>Celecoxib use for cancer prevention not recommended</td>
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<td>Other Cancer Sites</td>
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<td>Diclofenac sodium 3%</td>
<td>Topical application to skin in patients with actinic keratoses</td>
<td>Effective treatment: actinic keratoses (which are premalignant skin lesions)</td>
<td>GI side effects, rarely liver damage</td>
<td>U.S. FDA-approved gel</td>
<td>Recommend according to approved indication for cancer prevention by treating actinic keratoses</td>
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<tr>
<td>Imiquimod</td>
<td>Topical application to skin in patients with basal cell carcinoma, genital warts, actinic keratoses</td>
<td>Effective treatment of actinic keratoses (premalignant skin lesions)</td>
<td>Redness, itching, burning, bleeding of treated area; flaking, scaling, dryness, thickening of skin; swelling, stinging, pain in the treated area; blisters, scabs, bumps on the skin; headache, diarrhea, back pain; tiredness</td>
<td>U.S. FDA-approved cream</td>
<td>Recommend according to approved indication for cancer prevention by treating actinic keratoses</td>
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60% to 80% lifetime risk of breast cancer compared to 12% who have inherited harmful mutations.

### Prostate Cancer

Dutasteride and finasteride inhibit 5-α-reductase (5-AR), the enzyme that converts testosterone to its more potent form, 5-α-dihydrotestosterone. Both 5-AR inhibitors, already in use for treatment and management of lower urinary tract symptoms of benign prostatic hyperplasia (BPH) and for male pattern baldness, were shown to reduce prostate cancer (finasteride, by 24.8% in healthy men aged 55 years or older; dutasteride, by 22.8% in men at high risk based on age 50 to 75 years, elevated prostate-specific antigen [PSA], or a recent history of a prostate biopsy). Despite preventive efficacy in these two different populations (normal, older men and high-risk, older men), both agents share the troubling side effect of an increase in high-grade tumors among men who do develop prostate cancer while on the drug. As a result, the U.S. FDA has not approved either drug for prostate cancer risk reduction and in 2010 added a cautionary warning to their approved indications for symptomatic BPH and baldness.

### Colorectal Cancer

Epidemiologic data on aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) overwhelmingly point to an inverse relationship between use of these drugs and incidence of colorectal cancer (CRC). Aspirin use also is associated with a decrease in the incidence of adenomatous polyps, a precursor to CRC. In addition, aspirin reduces CRC incidence about 40% in individuals at increased risk because of carrying genetic variants predisposing to Lynch syndrome (hereditary nonpolyposis CRC). The major risks with NSAIDs are gastrointestinal and genitourinary bleeding, which increase with age. Significant increases in CV events have been seen with the cyclooxygenase-2 inhibitor.
(COX-2) selective inhibitors, celecoxib and rofecoxib, leading to removal of the latter drug from the market. Celecoxib, once approved for polyp reduction in the rare CRC-predisposing hereditary syndrome, familial adenomatous polyposis (FAP), no longer carries this risk-reducing indication. Combinations of agents at low doses, to reduce toxicity, are promising for CRC prevention. Low-dose sulindac, an NSAID, combined with difluoromethylornithine (DFMO), reduced the incidence of adenomas in patients with a history of adenomas in a phase II trial and is now being tested in 1,340 patients in a phase III randomized controlled trial (RCT) (http://clinicaltrials.gov/ct2/show/NCT01349881?term=NCT01349881&rank=1).

At present, the strongest evidence exists for aspirin as a medical intervention for CRC prevention. In discussing aspirin for this purpose, the PCC and patient must balance the predicted cancer prevention benefits against the risks. Although overall, studies have suggested an advantageous risk—benefit profile for aspirin use to reduce colon cancer incidence—this balance varies with age and other individual risk factors. Neither aspirin nor other NSAIDs are recommended for routine use in individuals at average risk. Because aspirin is already recommended to prevent CV disease in high-risk individuals and healthy individuals incur only a small increase in risk of nonfatal bleeding complications, the benefits are likely to outweigh the risks in most individuals, particularly in patients for whom antithrombotic therapy is indicated. Coprescription of a proton pump inhibitor offers an option to reduce bleeding complications. The uncertainties of dose and duration of aspirin use for prevention should also be discussed.

Other Cancers
Effective topical medicines have been approved for prevention of nonmelanoma skin cancers (see Table 4-1). In addition, extensive research into prevention of oral cancer in individuals with leukoplakia, a premalignant lesion, has shown that vitamin A derivatives, or retinoids, retard progression to invasive cancer. However, the toxicity associated with these agents has limited their use for this purpose. Finally, observational studies have shown that use of oral contraceptives confers long-term protection against ovarian cancer, although this has never been demonstrated in clinical trials.

**How can the primary care clinician use medical approaches to cancer prevention?**

Only tamoxifen, raloxifene, and a few topical agents are U.S. FDA-approved for risk reduction of cancer (breast cancer and skin cancer, respectively). The major concern for the PCC is that the preventive agent be safe, given that large numbers of healthy individuals must be treated prophylactically for many years in order that the risk of cancer is reduced in only a small number (see Fig. 4-1). Strategies to improve communication of clinical trial results are also being tested, with the hope of improving acceptance by PCCs and their patients of agents with proven advantageous risk: benefit profiles.

**References**


8. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and


