decreased the absolute risk of adenomatous polyp recurrence by 7% at 4 years; extended observational follow-up demonstrated a 12% absolute risk reduction 5 years after cessation of treatment. However, in the Women's Health Initiative, combined use of calcium carbonate and vitamin D twice daily did not reduce the incidence of invasive colorectal cancer compared with placebo after 7 years.

The Women's Health Initiative demonstrated that postmenopausal women taking estrogen plus progestin have a 44% lower relative risk of colorectal cancer compared to women taking placebo. Of >16,600 women randomized and followed for a median of 5.6 years, 43 invasive colorectal cancers occurred in the hormone group and 72 in the placebo group. The positive effect on colon cancer is mitigated by the modest increase in cardiovascular and breast cancer risks associated with combined estrogen plus progestin therapy.

A case-control study suggested that statins decrease the incidence of colorectal cancer; however, several subsequent case-control and cohort studies have not demonstrated an association between regular statin use and a reduced risk of colorectal cancer. No randomized controlled trials have addressed this hypothesis. A meta-analysis of statin use showed no protective effect of statins on overall cancer incidence or death.

CHEMOPREVENTION OF BREAST CANCER

Tamoxifen is an antiestrogen with partial estrogen agonistic activity in some tissues, such as endometrium and bone. One of its actions is to upregulate transforming growth factor β, which decreases breast cell proliferation. In randomized placebo-controlled trials to assess tamoxifen as adjuvant therapy for breast cancer, tamoxifen reduced the number of new breast cancers in the opposite breast by more than a third. In a randomized placebo-controlled prevention trial involving >13,000 pre- and postmenopausal women at high risk, tamoxifen decreased the risk of developing breast cancer by 49% (from 43.4 to 22 per 1000 women) after a median follow-up of nearly 6 years. Tamoxifen also reduced bone fractures; a small increase in risk of endometrial cancer, stroke, pulmonary emboli, and deep vein thrombosis was noted. The International Breast Cancer Intervention Study (IBIS-I) and the Italian Randomized Tamoxifen Prevention Trial also demonstrated a reduction in breast cancer incidence with tamoxifen use. A trial comparing tamoxifen with another selective estrogen receptor modulator, raloxifene, in postmenopausal women showed that raloxifene is comparable to tamoxifen in cancer prevention. This trial only included postmenopausal women. Raloxifene was associated with more invasive breast cancers and a trend toward more noninvasive breast cancers, but fewer thromboembolic events than tamoxifen; the drugs are similar in risks of other cancers, fractures, ischemic heart disease, and stroke. Both tamoxifen and raloxifene (the latter for postmenopausal women only) have been approved by the U.S. Food and Drug Administration (FDA) for reduction of breast cancer in women at high risk for the disease (1.66% risk at 5 years based on the Gail risk model: *http://www.cancer.gov/bcrisktool/*).

Because the aromatase inhibitors are even more effective than tamoxifen in adjuvant breast cancer therapy, it has been hypothesized that they would be more effective in breast cancer prevention. A randomized, placebo-controlled trial of exemestane reported a 65% relative reduction (from 5.5 to 1.9 per 1000 women) in the incidence of invasive breast cancer in women at elevated risk after a median follow-up of about 3 years. Common adverse effects included arthralgias, hot flashes, fatigue, and insomnia. No trial has directly compared aromatase inhibitors with selective estrogen receptor modulators for breast cancer chemoprevention.

CHEMOPREVENTION OF PROSTATE CANCER

Finasteride and dutasteride are 5-α-reductase inhibitors. They inhibit conversion of testosterone to dihydrotestosterone (DHT), a potent stimulator of prostate cell proliferation. The Prostate Cancer Prevention Trial (PCPT) randomly assigned men age 55 years or older at average risk of prostate cancer to finasteride or placebo. All men in the trial were being regularly screened with prostate-specific antigen (PSA) levels and digital rectal examination. After 7 years of therapy, the incidence of prostate cancer was 18.4% in the finasteride arm, compared with 24.4% in the placebo arm, a statistically significant difference. However, the finasteride group had more patients with tumors of Gleason score 7 and higher compared with the placebo arm (6.4 vs 5.1%). Reassuringly, long-term (10–15 years) follow-up did not reveal any statistically significant differences in overall mortality between all men in the finasteride and placebo arms or in men diagnosed with prostate cancer; differences in prostate cancer in favor of finasteride persisted.

Dutasteride has also been evaluated as a preventive agent for prostate cancer. The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial was a randomized double-blind trial in which approximately 8200 men with an elevated PSA (2.5–10 ng/mL for men age 50–60 years and 3–10 ng/mL for men age 60 years or older) and negative prostate biopsy on enrollment received daily 0.5 mg of dutasteride or placebo. The trial found a statistically significant 23% relative risk reduction in the incidence of biopsy-detected prostate cancer in the dutasteride arm at 4 years of treatment (659 cases vs 858 cases, respectively). Overall, across years 1 through 4, there was no difference between the arms in the number of tumors with a Gleason score of 7 to 10; however, during years 3 and 4, there was a statistically significant difference in tumors with Gleason score of 8 to 10 in the dutasteride arm (12 tumors vs 1 tumor, respectively).

The clinical importance of the apparent increased incidence of higher-grade tumors in the 5-α-reductase inhibitor arms of these trials is controversial. It may likely represent an increased sensitivity of PSA and digital rectal exam for high-grade tumors in men receiving these agents. The FDA has analyzed both trials, and it determined that the use of a 5-α-reductase inhibitor for prostate cancer chemoprevention would result in one additional high-grade (Gleason score 8 to 10) prostate cancer for every three to four lower-grade (Gleason score <6) tumors averted. Although it acknowledged that detection bias may have accounted for the finding, it stated that it could not conclusively dismiss a causative role for 5-α-reductase inhibitors. These agents are therefore not FDA-approved for prostate cancer prevention.

Because all men in both the PCPT and REDUCE trials were being screened and because screening approximately doubles the rate of prostate cancer, it is not known if finasteride or dutasteride decreases the risk of prostate cancer in men who are not being screened.

Several favorable laboratory and observational studies led to the formal evaluation of selenium and α-tocopherol (vitamin E) as potential prostate cancer preventives. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) assigned 35,533 men to receive 200 μg/d selenium, 400 IU/d α-tocopherol, selenium plus vitamin E, or placebo. After a median follow-up of 7 years, a trend toward an increased risk of developing prostate cancer was observed for those men taking vitamin E alone as compared to the placebo arm (hazard ratio 1.17; 95% confidence interval, 1.004–1.36).

VACCINES AND CANCER PREVENTION

A number of infectious agents cause cancer. Hepatitis B and C are linked to liver cancer; some HPV strains are linked to cervical, anal, and head and neck cancer; and *Helicobacter pylori* is associated with gastric adenocarcinoma and gastric lymphoma. Vaccines to protect against these agents may reduce the risk of their associated cancers.

The hepatitis B vaccine is effective in preventing hepatitis and hepatomas due to chronic hepatitis B infection.

A quadrivalent HPV vaccine (covering HPV strains 6, 11, 16, and 18) and a bivalent vaccine (covering HPV strains 16 and 18) are available for use in the United States. HPV types 16 and 18 cause cervical and anal cancer; reduction in these HPV types could prevent >70% of cervical cancers worldwide. HPV types 6 and 11 cause genital papillomas. For individuals not previously infected with these HPV strains, the vaccines demonstrate high efficacy in preventing persistent strain-specific HPV infections; however, the trials and substudies that evaluated the vaccines' ability to prevent cervical and anal cancer relied on surrogate outcome measures (cervical or anal intraepithelial neoplasia [CIN/AIN] I, II, and III), and the degree of durability of the immune response beyond 5 years is not currently known. The vaccines do not appear to impact preexisting infections and the efficacy appears to