TABLE 100-1 SUSPECTED CARCINOGENS

Carcinogens[a]	Associated Cancer or Neoplasm
Alkylating agents	Acute myeloid leukemia, bladder cancer
Androgens	Prostate cancer
Aromatic amines (dyes)	Bladder cancer
Arsenic	Cancer of the lung, skin
Asbestos	Cancer of the lung, pleura, peritoneum
Benzene	Acute myelocytic leukemia
Chromium	Lung cancer
Diethylstilbestrol (prenatal)	Vaginal cancer (clear cell)
Epstein-Barr virus	Burkitt's lymphoma, nasal T cell lymphoma
Estrogens	Cancer of the endometrium, liver, breast
Ethyl alcohol	Cancer of the breast, liver, esophagus, head and neck
Helicobacter pylori	Gastric cancer, gastric MALT lymphoma
Hepatitis B or C virus	Liver cancer
Human immunodeficiency virus	Non-Hodgkin's lymphoma, Kaposi's sarcoma, squamous cell carcinomas (especially of the urogenital tract)
Human papilloma virus	Cancers of the cervix, anus, oropharynx
Human T cell lymphotropic virus type 1 (HTLV-1)	Adult T cell leukemia/lymphoma
Immunosuppressive agents (azathioprine, cyclosporine, glucocorticoids)	Non-Hodgkin's lymphoma
Ionizing radiation (therapeutic or diagnostic)	Breast, bladder, thyroid, soft tissue, bone, hematopoietic, and many more
Nitrogen mustard gas	Cancer of the lung, head and neck, nasal sinuses
Nickel dust	Cancer of the lung, nasal sinuses
Diesel exhaust	Lung cancer (miners)
Phenacetin	Cancer of the renal pelvis and bladder
Polycyclic hydrocarbons	Cancer of the lung, skin (especially squamous cell carcinoma of scrotal skin)
Radon gas	Lung cancer
Schistosomiasis	Bladder cancer (squamous cell)
Sunlight (ultraviolet)	Skin cancer (squamous cell and melanoma)
Tobacco (including smokeless)	Cancer of the upper aerodigestive tract, bladder
Vinyl chloride	Liver cancer (angiosarcoma)

[a]Agents that are thought to act as cancer initiators and/or promoters.

CHEMOPREVENTION OF CANCERS OF THE UPPER AERODIGESTIVE TRACT

Smoking causes diffuse epithelial injury in the oral cavity, neck, esophagus, and lung. Patients cured of squamous cell cancers of the lung, esophagus, oral cavity, and neck are at risk (as high as 5% per year) of developing second cancers of the upper aerodigestive tract. Cessation of cigarette smoking does not markedly decrease the cured cancer patient's risk of second malignancy, even though it does lower the cancer risk in those who have never developed a malignancy. Smoking cessation may halt the early stages of the carcinogenic process (such as metaplasia), but it may have no effect on late stages of carcinogenesis. This "field carcinogenesis" hypothesis for upper aerodigestive tract cancer has made "cured" patients an important population for chemoprevention of second malignancies.

Oral human papilloma virus (HPV) infection, particularly HPV-16, increases the risk for cancers of the oropharynx. This association exists even in the absence of other risk factors such as smoking or alcohol use (although the magnitude of increased risk appears greater than additive when HPV infection and smoking are both present). Oral HPV infection is believed to be largely sexually acquired. Although no direct evidence currently exists to confirm the hypothesis, the introduction of the HPV vaccine may eventually reduce oropharyngeal cancer rates.

Oral leukoplakia, a premalignant lesion commonly found in smokers, has been used as an intermediate marker of chemopreventive activity in smaller shorter-duration, randomized, placebo-controlled trials. Response was associated with upregulation of retinoic acid receptor-β (RAR-β). Therapy with high, relatively toxic doses of isotretinoin (13-*cis*-retinoic acid) causes regression of oral leukoplakia. However, the lesions recur when the therapy is withdrawn, suggesting the need for long-term administration. More tolerable doses of isotretinoin have not shown benefit in the prevention of head and neck cancer. Isotretinoin also failed to prevent second malignancies in patients cured of early-stage non-small cell lung cancer; mortality rates were actually increased in current smokers.

Several large-scale trials have assessed agents in the chemoprevention of lung cancer in patients at high risk. In the α-tocopherol/β-carotene (ATBC) Lung Cancer Prevention Trial, participants were male smokers, age 50–69 years at entry. Participants had smoked an average of one pack of cigarettes per day for 35.9 years. Participants received α-tocopherol, β-carotene, and/or placebo in a randomized, two-by-two factorial design. After median follow-up of 6.1 years, lung cancer incidence and mortality were statistically significantly increased in those receiving β-carotene. α-Tocopherol had no effect on lung cancer mortality, and no evidence suggested interaction between the two drugs. Patients receiving α-tocopherol had a higher incidence of hemorrhagic stroke.

The β-Carotene and Retinol Efficacy Trial (CARET) involved 17,000 American smokers and workers with asbestos exposure. Entrants were randomly assigned to one of four arms and received β-carotene, retinol, and/or placebo in a two-by-two factorial design. This trial also demonstrated harm from β-carotene: a lung cancer rate of 5 per 1000 subjects per year for those taking placebo and of 6 per 1000 subjects per year for those taking β-carotene.

The ATBC and CARET results demonstrate the importance of testing chemoprevention hypotheses thoroughly before their widespread implementation because the results contradict a number of observational studies. The Physicians' Health Trial showed no change in the risk of lung cancer for those taking β-carotene; however, fewer of its participants were smokers than those in the ATBC and CARET studies.

CHEMOPREVENTION OF COLON CANCER

Many colon cancer prevention trials are based on the premise that most colorectal cancers develop from adenomatous polyps. These trials use adenoma recurrence or disappearance as a surrogate endpoint (not yet validated) for colon cancer prevention. Early clinical trial results suggest that nonsteroidal anti-inflammatory drugs (NSAIDs), such as piroxicam, sulindac, and aspirin, may prevent adenoma formation or cause regression of adenomatous polyps. The mechanism of action of NSAIDs is unknown, but they are presumed to work through the cyclooxygenase pathway. Although two randomized controlled trials (the Physicians' Health Study and the Women's Health Study) did not show an effect of aspirin on colon cancer or adenoma incidence in persons with no previous history of colonic lesions after 10 years of therapy, these trials did show an approximately 18% relative risk reduction for colonic adenoma incidence in persons with a previous history of adenomas after 1 year. Pooled findings from observational cohort studies do demonstrate a 22% and 28% relative reduction in colorectal cancer and adenoma incidence, respectively, with regular aspirin use, and a well-conducted meta-analysis of four randomized controlled trials (albeit primarily designed to examine aspirin's effects on cardiovascular events) found that aspirin at doses of at least 75 mg resulted in a 24% relative reduction in colorectal cancer incidence after 20 years, with no clear increase in efficacy at higher doses. Cyclooxygenase-2 (COX-2) inhibitors have also been considered for colorectal cancer and polyp prevention. Trials with COX-2 inhibitors were initiated, but an increased risk of cardiovascular events in those taking the COX-2 inhibitors was noted, suggesting that these agents are not suitable for chemoprevention in the general population.

Epidemiologic studies suggest that diets high in calcium lower colon cancer risk. Calcium binds bile and fatty acids, which cause proliferation of colonic epithelium. It is hypothesized that calcium reduces intraluminal exposure to these compounds. The randomized controlled Calcium Polyp Prevention Study found that calcium supplementation