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An estimated 1.53 million new cases of invasive cancer and 569,490 cancer deaths will occur in the United States in 2010 [see Figure 1].<sup>1</sup> An additional 2,000,000 cases of superficial squamous cell and basal cell carcinomas will also be diagnosed, but these rarely result in death. Recently surpassing heart disease, cancer is now the leading cause of death for men and women younger than 80 years in the United States, accounting for one in four deaths.<sup>1</sup> Nonetheless, the overall age-adjusted cancer mortality rate has declined since the early 1990s, reversing the rising cancer mortality of preceding decades [see Figure 2].<sup>2</sup> Similar trends have been reported in Europe.<sup>3</sup> Worldwide, cancer control is becoming increasingly important as life expectancy improves because of lower infant mortality and fewer deaths from infectious diseases.

Morbidity and mortality from many forms of cancer can be controlled through primary or secondary prevention. Primary prevention can be defined as risk modification to lower cancer occurrence. Secondary prevention refers to the use of screening tests to detect cancers at earlier stages. Chemoprevention—the use of medications to inhibit or reverse the carcinogenic process—is being studied as another approach to reduce cancer rates. Effective chemopreventive agents have been discovered for reducing the incidence of breast cancer in women, the occurrence of second cancers in patients with oral cancers, and for the occurrence of colorectal cancers in susceptible patients.<sup>4–6</sup> In addition, finasteride has shown significant risk reduction in prostate cancer.<sup>7</sup>

## Environmental Carcinogens

Up to 90% of all cancers in the United States may primarily be the result of environmental factors.<sup>8</sup> This conclusion is based on evidence that incidence rates of specific cancers change over time, differ substantially among populations, and can be altered by migration. Environment encompasses a person's way of life, including occupation, diet, tobacco use, alcohol consumption, and sun exposure. Alterations of the environment may be sufficient to prevent most cancers, but heredity also exerts an influence on the multistage development of human cancers.

Conclusive evidence regarding the etiologic role of specific environmental factors is difficult to obtain in studies of humans because (1) the time between a carcinogenic exposure and diagnosis of a resultant cancer is usually years or decades, (2) the amount of exposure to a carcinogen can rarely be quantified accurately in retrospect, and (3) most carcinogens induce cancer in only a small proportion of

exposed persons.<sup>9</sup> The role of complex dietary factors in cancer development is particularly difficult to study for these reasons. However, data are available from large epidemiologic studies that employ a prospective study design, careful measurement of dietary intake, and bioassays as dosimeters of nutrients consumed. Evidence suggests that obesity and diets characterized by high caloric intake, increased consumption of red meat and animal fat, and decreased consumption of fruits and vegetables increase the risk of cancers of the breast, colon, lung, pancreas, oral cavity, and other organs. However, the specific ingredients in the diet that elevate or lower cancer risk have been difficult to identify.<sup>9</sup>

Clinicians often discover the link between an unusual carcinogenic exposure and exceptional risk of a rare cancer. Carcinogens that have been identified in this way include the hormone diethylstilbestrol and the industrial chemicals bis(chloromethyl) ether and vinyl chloride. Most cancers, however, arise as a result of fairly common exposures that may produce only moderate elevations in risk. To detect these associations, epidemiologists strive for large study populations, accurate exposure measurement, informed judgments regarding the relevant temporal relation between exposure and cancer diagnosis, and recognition of confounding (extraneous) causes of the cancer under study.<sup>10</sup> Despite inherent difficulties in studying human populations, epidemiologic methodology remains the most useful method for studying carcinogenic effects in humans. A causal relation between a suspected carcinogen and cancer is strengthened by corroborating studies that provide plausible biologic mechanisms.

Certain physical, chemical, and biologic agents have been identified as carcinogens.<sup>9</sup> These agents may act on a single organ or at multiple sites [see Table 1]. Ultraviolet radiation from sunlight can cause cutaneous melanoma, basal cell carcinoma, and squamous cell carcinoma, whereas ionizing radiation can induce leukemias, sarcomas, and carcinomas at various sites.<sup>11</sup> Several dozen chemicals are known to be carcinogenic in humans; they induce leukemias, lymphomas, and carcinomas of diverse organs, particularly of the lung and upper airway. Many more chemical compounds can induce cancer in laboratory animals, but evidence linking these compounds to cancer in humans is insufficient or inconsistent. Strong evidence of viral oncogenesis in humans has been found for hepatitis B and C viruses in patients with liver cancer, human papillomavirus in cervical and anal cancers, Epstein-Barr virus (EBV) in nasopharyngeal cancer and in some lymphomas, and human herpesvirus type 8 (HHV-8) in Kaposi sarcoma.<sup>12,13</sup> The discovery that *Helicobacter pylori* causes gastric adenocarcinoma and certain lymphomas represents the first time a bacterium has been linked to the etiology of malignancy, and this is significant because it suggests that antibiotics may be used for the prevention and treatment of certain malignancies.<sup>14,15</sup>

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Table 1 Established Causes of Human Cancer

	Carcinogens	Cancers
Chemicals and naturally occurring compounds	Aflatoxins, naturally occurring Aluminum production 4-Aminobiphenyl Arsenic Asbestos Benzene Benzidine Beryllium Bis(chloromethyl) ether Cadmium Chromium compounds Erionite Ethylene oxide Formaldehyde Mustard gas 2-Naphthylamine Nickel compounds Radon Silica Sulfur mustard Sunlight (UV) Tetrachlorodibenzo- <i>p</i> -dioxin Vinyl chloride	Liver Lung, bladder Bladder Lung, skin, bladder Lung, mesothelioma of pleura and peritoneum, larynx, ovary Acute leukemia, multiple myeloma, non-Hodgkin lymphoma Bladder Lung Lung Prostate, respiratory tract, genitourinary tract Lung Mesothelioma Leukemia Nasopharynx, leukemia Pharynx, lung Bladder Lung, nasal sinuses Lung Lung Lung Skin, melanoma, eye Lymphoma, sarcoma Liver (angiosarcoma and HCC)
Medicines and hormones	Azathioprine Busulfan, treosulfan Chlorambucil Cyclophosphamide Cyclosporine Estrogens Etoposide Ionizing radiation Melphalan Methoxsalen with psoralen plus ultraviolet A therapy (PUVA) Nitrosourea Phenacetin Plants with aristolochic acid Semustine Tamoxifen Thiotepa	Lymphoma, skin Leukemia Leukemia Bladder, leukemia Lymphoma, skin, other Endometrium, breast, ovary Leukemia Leukemia, breast, thyroid, lung, bone, other Leukemia Basal cell and squamous cell skin cancers  Leukemia Renal pelvis, bladder Renal pelvis, ureter Leukemia Endometrium Leukemia
Infectious agents	<i>Clonorchis sinensis</i> Epstein-Barr virus  <i>Helicobacter pylori</i> Hepatitis B and C viruses Human herpesvirus type 8 Human T cell lymphotropic virus type I Human papillomavirus types 16 and 18 <i>Opisthorchis viverrini</i> <i>Schistosoma haematobium</i>	Cholangiocarcinoma Nasopharynx, lymphomas (Burkitt, Hodgkin, non-Hodgkin, NK/T cell lymphoma) Stomach, MALT Liver Kaposi sarcoma, primary effusion lymphoma Adult T cell leukemia/lymphoma Cervix, anus, oral cavity, Liver Bladder
Mixtures	Alcohol Betel quid Coal tars Involuntary smoking Leather dust Mineral oils Salted fish Shale oils Soot Tobacco  Wood dust	Liver, esophagus, pharynx, larynx Mouth Skin, lung Lung Nasal sinuses Skin Nasopharynx Skin Skin, lung Lung, mouth, pharynx, larynx, esophagus, stomach, pancreas, bladder, kidney, renal pelvis, cervix Nasal sinuses

Adapted from IARC Monographs Database on Carcinogenic Risks to Humans. Available at: [www.iarc.fr/en/websites/databases.php](http://www.iarc.fr/en/websites/databases.php)  
HCC = hepatocellular carcinoma; MALT = mucosa-associated lymphoid tissue; NK = natural killer; UV = ultraviolet.

During the past 10 years, biomarkers have been increasingly used to enhance exposure assessment, gain insights into disease mechanisms, and identify host susceptibility. Epidemiology has traditionally employed a quantitative approach rather than mechanistic steps to the understanding of disease causation. With the advent of modern molecular techniques, molecular epidemiologists can investigate the molecular pathogenesis of cancer. Biomarkers used in cancer epidemiology may be broadly classified into categories according to study design and may include markers of internal dose, biologically effective dose, early biologic effects, susceptibility, and disease.<sup>16</sup> Examples of common biomarkers include DNA adducts, polymorphisms in metabolic genes, and cytogenetic alterations and mutations in cancer cells.<sup>17–20</sup> Validated biomarkers can be useful for exposure assessment when traditional tools are not effective for identifying susceptible and exposed persons. For example, insulin-like growth factor-1 (IGF-1) and its main binding protein, IGFBP-3, have been investigated as potential risk markers for a variety of common cancers.<sup>21–24</sup> Studies show that high circulating IGF-1 and low IGFBP-3 concentrations are correlated with an increased risk of cancers of the colon, prostate, and lung, as well as premenopausal breast cancer. IGF-1 appears to promote tissue growth and prevent apoptosis, whereas IGFBP-3 modulates IGF-1 availability and induces apoptosis via an IGF-independent mechanism.<sup>25</sup> Although IGF-1 is not elevated in patients with early B-cell chronic lymphocytic leukemia, it is a prognostic factor for disease progression.<sup>26</sup>

#### TOBACCO

Tobacco is by far the major cause of lung cancer worldwide, particularly in developing nations.<sup>27–29</sup> In the United States, 30% of all cancer deaths are attributed to tobacco use.<sup>30</sup> Tobacco use is associated primarily with squamous cell and small cell carcinomas of the lung, as well as with pulmonary adenocarcinomas. Increased tobacco consumption in the United States and elsewhere has been followed by a rise in lung cancer rates several decades later. A series of reports from the surgeon general have summarized data from individual epidemiologic studies.<sup>31</sup> At least nine large prospective studies of up to 1,000,000 persons each and 50 case-control studies worldwide have consistently shown that cigarette smoking increases the risk of lung cancer. This increased risk is related to the dose of smoking as measured by years of tobacco use, amount of tobacco consumed daily, tar and nicotine content of the cigarettes, and depth of inhalation of cigarette smoke. Programs that promote reductions in tobacco use among adolescents and young adults, if addressed to these age groups, can prove effective because most smokers become addicted to cigarettes at an early age.<sup>32,33</sup> With smoking cessation, the risk decreases, although more than a decade is required to return to the low cancer risk level of nonsmokers; thus, both prevention and early cessation of tobacco use are important.<sup>34</sup>

Cigarette smoking and alternative methods of tobacco use increase the risk of laryngeal and oral cancers.<sup>31</sup> Fewer lung cancers develop in pipe and cigar smokers than in cigarette smokers, but pipe and cigar smokers are at high risk for oral mucosal cancers, including lip cancer in pipe users.<sup>35</sup> Use of smokeless tobacco also places individuals at high risk for

cancer of the oral mucosa.<sup>31</sup> Long-term exposure to environmental tobacco smoke (passive smoking) has been associated with a 30% increased risk of lung cancer in nonsmokers and is estimated to account for 3,000 cases of lung cancer in the United States each year. The Third National Health and Nutrition Examination Survey reported in 1996 that 88% of a large population sample of nonsmokers had detectable levels of serum cotinine, a surrogate measure of tobacco exposure.<sup>36</sup> Furthermore, the effects of passive smoking have been demonstrated in pet dogs that are at increased risk for certain malignancies only when their owners smoke.<sup>37</sup>

The causal effect between tobacco use and cancers of the lung and the head and neck is well established; however, tobacco also plays a major carcinogenic role in other organs of the upper aerodigestive tract. Notable among these is the esophagus, for which cigarette smoking is the major risk factor for cancer, particularly squamous cell carcinoma of the esophagus. Over the past three decades, there has been an increasing incidence of adenocarcinoma in the lowest third of the esophagus that is associated with a condition known as Barrett esophagus. Currently, this malignancy constitutes more than 50% of esophageal cancers. Although associated with tobacco use, Barrett esophagus generally has been more closely linked to gastroesophageal reflux disease (GERD).<sup>38–40</sup>

Alcohol consumption increases the risk of cancers of the oral cavity and the head and neck, as well as cancers of the esophagus, but the risk is greatly increased when alcohol consumption is associated with tobacco use. Cigarette smoking and alcohol consumption are independent risk factors for oral cancer, and their combined use results in a synergistic effect that has been associated with a 13-fold increase in risk in some studies.<sup>41,42</sup>

Tobacco also plays a significant etiologic role in renal cell carcinoma, bladder cancer, pancreatic cancer, cervical cancer, and gastric cancer. In each of these, the relative risk ranges between 1.5 and 3. Although the association between cigarette smoking and colorectal cancer is controversial, the causal association has been more accepted recently.<sup>43,44</sup> Also controversial is the role of tobacco use in the development of breast cancer in women.<sup>45,46</sup>

Reduction in tobacco use is clearly the most important approach to cancer prevention. Physicians see approximately 85% of smokers in their offices at least once a year and can effectively help their patients to stop smoking by using structured, short-term counseling techniques administered by the physicians themselves or their office staff. Smoking cessation efforts employ behavior modification techniques that have been successful with other addictive disorders; nicotine substitutes (e.g., patch or gum) have also been effective for selected patients. Relapse rates within the first year after cessation are high, and often many attempts to quit are required.<sup>30</sup> In men, the prevalence of smoking decreased from 52% to 27% between 1965 and 1995, and the incidence of lung cancer has declined since rates peaked in 1984.<sup>1</sup> In women, smoking prevalence has decreased from 34% to 20%, whereas lung cancer incidence has yet to decline.<sup>1</sup>

Policy approaches to tobacco control include restrictions on advertising that targets young people, aggressive anti-smoking education at the elementary school level, limits on government subsidies to tobacco growers, and taxation to

raise the prices of tobacco and tobacco products. Many communities have legislation requiring smoke-free workplaces, restaurants, and other facilities.<sup>47</sup> In 1998, a master settlement agreement was signed by 46 state attorneys general, a coalition of trial lawyers, and representatives of the five largest tobacco manufacturers in the United States. The

settlement requires the tobacco companies to reimburse the states over \$200 billion over 25 years for the cost of providing health care services to people with tobacco-related diseases.<sup>48</sup> It also prohibits targeting of youths by banning cartoon characters in advertising, sponsorship of certain events, and use of certain promotional tactics, such as the

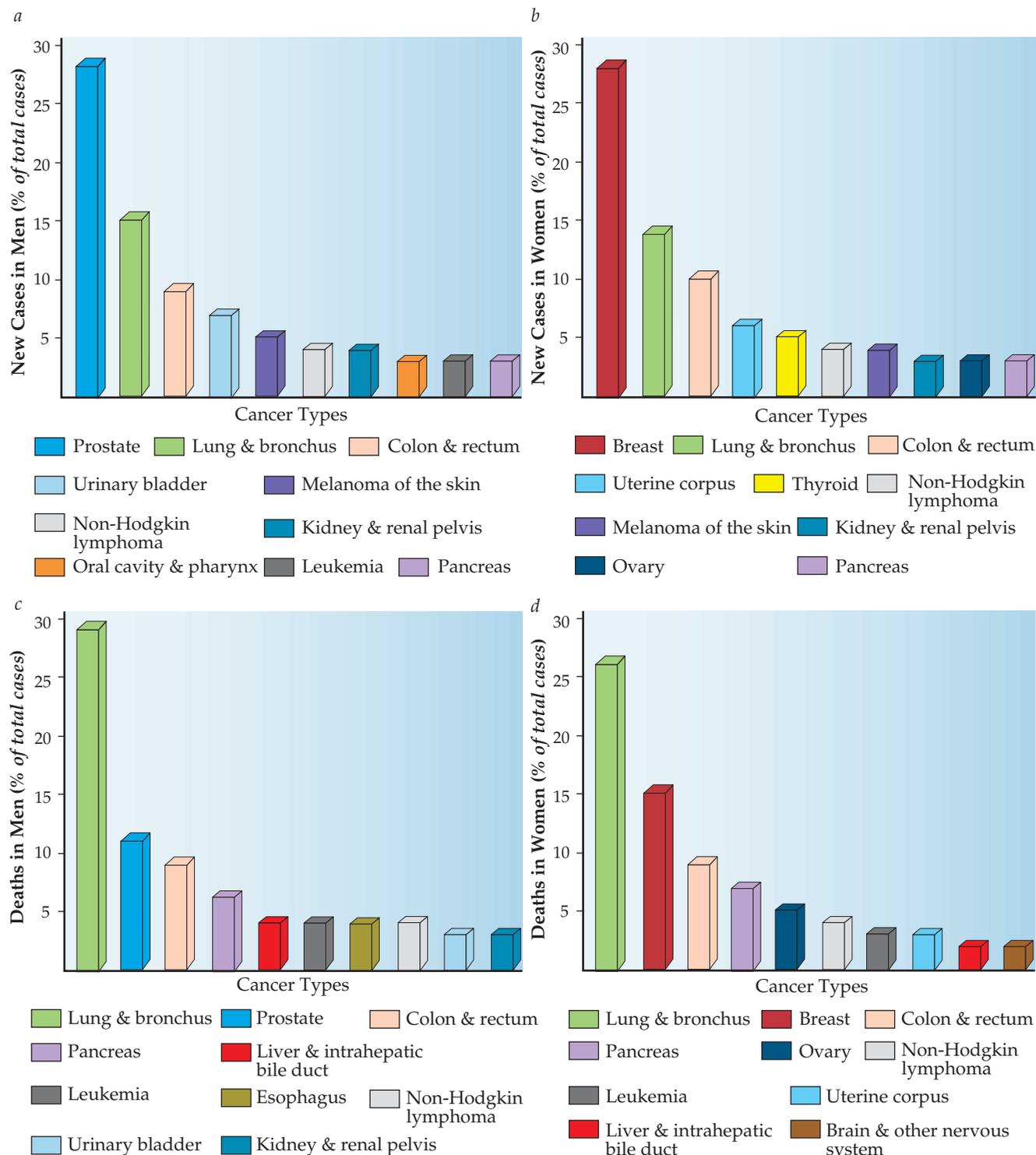


Figure 1 Estimated new cancer cases in (a) men and (b) women and estimated deaths in (c) men and (d) women. Data are from Jemal and colleagues<sup>1</sup> and exclude skin cancer from basal and squamous cells and in situ carcinoma with the exception of urinary bladder.

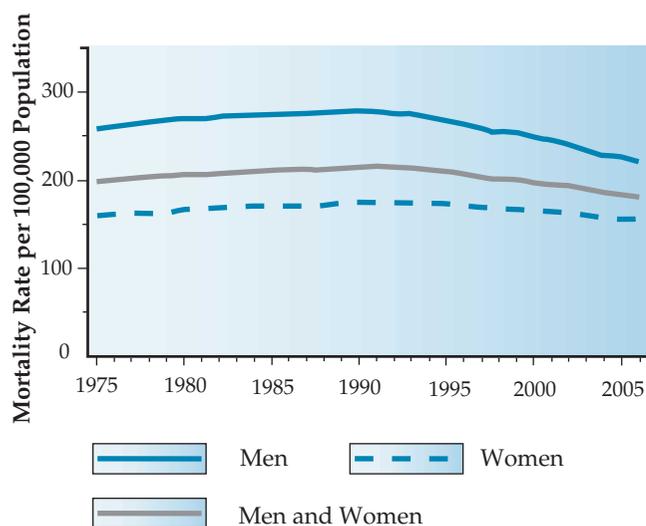


Figure 2 Annual death rates from cancer in the United States from 1975 to 2006. Data from Jemal and colleagues.<sup>1</sup>

targeting of adolescents. Additional lawsuits at the state level, including a successful suit in Florida, have found tobacco companies liable for cancer and other diseases in smokers.<sup>49</sup>

In recent years, governmental intervention has influenced tobacco cessation by banning smoking in public spaces, such as restaurants, bars, and beaches. In addition, increasing cigarette taxes has a definite effect on reducing tobacco use in young adults. Such policies are being tested in India and China to decrease global tobacco-related diseases.<sup>29</sup>

#### DIET

Unusual geographic clustering has been observed for certain cancers of the digestive tract. Exceptionally high mortality rates are found for esophageal cancer in southern Africa and in parts of China and for stomach cancer in eastern Asia and eastern Europe. In the United States, nearly one fifth of all cancers arise in the digestive tract, most often in the colon or rectum. For unknown reasons, cancers of the right colon have become more common, whereas sigmoid colon and rectal cancers have diminished. Death rates from stomach cancer in the United States have declined sharply over the past 70 years, possibly because of improvements in food preservation and decreased consumption of salted, pickled, and smoked foods.<sup>50</sup> Incidence rates of certain digestive tract cancers change when people migrate and, as a result, modify their diets. For example, Japanese who migrate to the United States have a decline in stomach cancer rates, but their colon cancer rates rise within one generation to the levels found in the American-born white population.<sup>50,51</sup> Within the United States, colon cancer rates differ among subpopulations. Mormons and Seventh-Day Adventists, who tend to consume less meat, have lower rates of large bowel cancer. Mexican Americans have low rates of bowel cancer but high rates of stomach cancer.

Despite epidemiologic evidence implicating diet in digestive tract cancer, the roles of specific dietary elements

remain uncertain. Suspected dietary factors in large bowel cancer include excess consumption of animal fat and red meat and excess total caloric intake.<sup>52-54</sup> Although low fiber consumption has been suggested to increase colorectal cancer risk, a randomized trial and other recent studies did not show any benefit of a high-fiber, low-fat diet in reducing the recurrence of colorectal adenomas.<sup>55-57</sup>

Recommended dietary changes to reduce cancer risk include controlling caloric intake, decreasing fat consumption to less than 30% of total daily caloric intake, and increasing consumption of fresh fruits and vegetables.<sup>53</sup> These dietary modifications may also reduce the risk of cardiovascular disease.

In general, despite widespread public interest and concern regarding the role of diet in cancer etiology, specific recommendations regarding appropriate dietary recommendations remain elusive. A major contribution in this regard is a monograph published by the World Health Organization that summarizes much of the current knowledge regarding the association between diet and cancer prevention.<sup>58</sup> Generally, a diet high in fresh fruits and vegetables and low in red meat seems most prudent. Much interest currently focuses on caloric consumption, physical activity, and energy use and how these factors contribute to obesity and cancer risk [see Obesity and Physical Inactivity, below]. Very recently, attention has focused on early-life patterns of food and caloric consumption and their role in establishing future cancer risk.

Numerous randomized trials have been undertaken to clarify the relationship between diet and cancer. Antioxidant vitamins, minerals such as selenium and calcium, low-fat diets, and other dietary patterns have been assessed as possible risk-lowering factors. Results have differed across these studies, and many studies are ongoing. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial randomized 29,133 Finnish male smokers to receive vitamin E,  $\beta$ -carotene, both, or a placebo to determine whether these supplements lowered the risk of lung cancer. Ironically, the study showed an 18% increased risk of lung cancer in patients who received  $\beta$ -carotene.<sup>59</sup> A postintervention follow-up study concluded that smokers should avoid  $\beta$ -carotene supplements.<sup>60</sup> These results suggest that dietary interventions may be harmful, and careful investigation is needed to determine their role in cancer prevention.<sup>61</sup> In the SELECT trial, a multinational, randomized, and placebo-controlled trial, selenium and vitamin E did not prevent prostate cancer in relatively healthy men.<sup>62</sup>

#### OBESITY AND PHYSICAL INACTIVITY

Two risk factors for cancer that have come under increased study in recent years have been obesity and physical inactivity, which are related to energy intake and consumption. A study by Calle and colleagues demonstrated that obesity, which has been associated most notably with breast cancer and endometrial cancer, may be linked to a larger number of cancers than had previously been suspected, including colon, rectum, prostate, pancreas, kidney, and others.<sup>63</sup> An association with adenocarcinoma of the esophagus by increasing GERD has also been fairly consistent. Although

the physiologic mechanisms linking obesity to hormonally related cancers (e.g., breast cancer and prostate cancer) are well elucidated, the biologic underpinnings between obesity and other cancers are not obvious.

Physical inactivity, which frequently accompanies obesity, has been implicated as a risk factor in many chronic diseases and is currently being assessed for its contribution to cancer risk. A Canadian study showed that physical inactivity, high energy intake, and obesity are associated with an increased risk of rectal cancer; the study further suggested that these three factors may have a synergistic effect that further increases cancer risk if they are all present.<sup>64</sup>

Increased physical activity, either on an occupational or a recreational basis, has been shown to be a protective factor for a number of malignancies, including colorectal and breast cancer.<sup>65</sup> Whether this represents a surrogate for a healthy lifestyle, whether it serves to counteract some of the deleterious effects of obesity, or whether some other physiologic mechanisms are at work remains unclear. Nonetheless, randomized trials are under way to assess its efficacy as a modifiable intervention for cancer prevention in persons at high risk for developing certain cancers.

#### INFECTIOUS AGENTS

Infectious agents have been known to cause cancer since 1911, when Peyton Rous discovered the Rous sarcoma virus. However, recent findings have made it clear that infectious agents are responsible for a larger portion of the cancer burden in the United States and around the world than was previously suspected. This is a cause for optimism because it suggests that the preventive and management strategies developed for controlling infectious diseases, including sanitation, vaccination, antibiotics, and antivirals, may be applicable to cancer prevention.

Hepatitis B virus (HBV) infection is an established risk factor for the development of liver cancer in certain patient populations. Cancers of the liver, primarily hepatocellular carcinoma (HCC), are relatively rare in the United States, but the rates are rising.<sup>66</sup> HCC occurs largely in patients with cirrhosis caused by chronic hepatitis, hemochromatosis, and the use of exogenous androgenic steroids. It also may occur as a result of occupational exposure to vinyl chloride and the subsequent development of angiosarcoma of the liver. Liver cancer is a leading cause of cancer death in certain developing nations, particularly in Africa and Asia. The major risk factor for liver cancer in these patients is chronic HBV infection, which is often acquired during infancy or early childhood. The risk of liver cancer is increased as much as 200-fold in HBV carriers. Hepatitis B vaccination decreases the risk of infection and subsequent occurrence of HCC. Since the initiation of wide-scale hepatitis B vaccination in Taiwan, HCC rates have fallen by 25% or more.<sup>67,68</sup> In the United States, however, the rising incidence of hepatitis C virus (HCV), which causes hepatoma and for which a vaccine does not yet exist, poses an increasing problem.<sup>69</sup>

Squamous cell carcinoma of the uterine cervix has been linked to human papillomavirus (HPV)<sup>70,71</sup> and has been studied in relation to sexual behavior. The incidence of the disease is increased in prostitutes and in other women who have multiple sexual partners, in women who have

first coitus at an early age, and in women with a history of venereal disease. Cohort and case-control studies have demonstrated that HPV is associated with both in situ and invasive cervical carcinoma. HPV DNA has been found in up to 95% of cervical cancers. Furthermore, progression of cervical intraepithelial neoplasia is associated with high levels of HPV DNA within the cervical tissues.

This finding has prompted two advances in the prevention and early detection of cervical cancer. First, the presence of HPV in the genital mucosa of women is now being used as a means for cervical cancer screening.<sup>72</sup> This technique has proved to be inexpensive and effective and has a high enough sensitivity and specificity for use in poor countries, where the more commonly used Papanicolaou smear is not routinely available. Women are able to swab themselves; the swab is tested for the presence of HPV DNA, and its presence is then used to select those women for further testing where routine gynecologic care is not feasible.<sup>73</sup>

A second major advance linked to the viral etiology of cervical cancer is the development of a vaccine for HPV. Approximately 70% of cervical cancer is caused by sexual transmission of HPV types 16 and 18. Efforts have been made to develop vaccines that could confer protection against infection by these HPV types, thereby reducing the incidence of preinvasive lesions that eventually lead to invasive cervical cancer. These vaccines are made with viruslike particles that express only the HPV L1 protein but are non-infectious and highly immunogenic. Two products have been studied thus far: a quadrivalent vaccine against HPV types 6, 11, 16, and 18 (types 6 and 11 being responsible for the majority of genital warts) and a bivalent vaccine against HPV types 16 and 18, which may also confer cross-protection against HPV types 31 and 45.<sup>74,75</sup> In two randomized trials, both vaccines appeared to be highly effective in preventing HPV infection, conferring protection up to 4.5 years after the administration of three doses over a 6-month period.<sup>74,75</sup> The quadrivalent vaccine (Gardasil) was approved by the Food and Drug Administration as a cancer prevention agent for patients 9 to 26 years of age; studies of the bivalent vaccine are ongoing.<sup>70</sup>

Two phase III studies have confirmed Gardasil to be highly effective in providing protection from cervical cancer. In the first study, the vaccine provided 100% protection from cervical, vaginal, and vulvar diseases caused by HPV types 6, 11, 16, and 18.<sup>76</sup> In the second study, Gardasil provided 98% protection against advanced cervical precancerous lesions caused by the two primary cancer-causing HPV types, 16 and 18.<sup>77</sup>

In addition to cervical cancer, HPV is also implicated in a subgroup of head and neck squamous cell carcinoma (HNSCC), particularly in the oropharynx region, and tends to affect young patients without excessive exposure to tobacco and alcohol.<sup>78</sup> Two viral oncogenes, *E6* and *E7*, from HPV type 16 infection, are associated with the malignant transformation.<sup>79</sup> HPV-associated HNSCC has a better prognosis and response to treatment compared with HPV-negative HNSCC.<sup>80,81</sup>

Another virus of interest as a carcinogen is EBV. This DNA virus has been associated with a number of different malignancies, including nasopharyngeal carcinoma, Burkitt

lymphoma, posttransplant lymphoproliferative disease, and possibly Hodgkin disease.

Particularly since the early 1980s, with the onset of AIDS and the HIV era, interest has focused on finding retroviruses or RNA viruses associated with cancer. This has been of particular interest because many of the oncogenic viruses found in rodent and animal studies (e.g., SV40 or Rous sarcoma virus) are RNA viruses. A major breakthrough in this regard was the discovery that HHV-8, a retrovirus, was the etiologic agent for Kaposi sarcoma.<sup>82</sup> Kaposi sarcoma, which classically occurs in elderly men of Mediterranean descent, became more widespread as a cancer commonly found in AIDS patients. Moore and Chang found HHV-8 to be the virus responsible for Kaposi sarcoma in both the AIDS-associated and the classic forms of the disease.<sup>82</sup> HHV-8 has been found to be responsible for Castleman disease and other lymphomas as well.

Human T cell lymphotropic virus type I (HTLV-I) infection has been linked to the development of an aggressive form of leukemia, adult T cell leukemia/lymphoma.<sup>83</sup> This disease has an unusual geographic distribution, with clusters in Japan and the Caribbean, and a prolonged latency period. Spatial and temporal clusters of leukemia and Hodgkin disease have also been reported, but no etiologic agent has been found, and these clusters may be the result of chance. HIV type 1 (HIV-1) has been identified as the cause of AIDS. Patients with AIDS are at high risk for Kaposi sarcoma, Hodgkin disease, non-Hodgkin lymphoma (NHL), and other cancers.

In recent years, the incidence of NHL has increased in adolescents and adults. Both inherited and acquired immunodeficiency appear to be associated with an elevated risk of NHL. Organ transplant recipients are at high risk for NHL and carcinomas of the skin.<sup>84</sup> These neoplasms may appear within several weeks after renal or cardiac transplantation and therefore differ from most environmentally induced cancers that arise many years after exposure to carcinogens. The transplant-associated lymphomas have a predilection for the central nervous system. Immunosuppressive therapy with azathioprine and cyclosporine has been implicated as a risk factor in transplant recipients, although the transplanted cells per se may also have a carcinogenic influence. EBV has been associated with nasopharyngeal cancer, Burkitt lymphoma, NHL, and Hodgkin disease.<sup>12</sup>

Evidence accrued over the past 20 years has established *H. pylori* as a causal agent in gastric cancer. This discovery is significant because it represents the first time a bacterium has been found to be associated with cancer etiology. *H. pylori* infection is a widely prevalent infection that increases the risk of gastric adenocarcinoma and gastric lymphoma of mucosa-associated lymphoid tissue (MALT) lymphomas.<sup>14,15</sup> The treatment of *H. pylori* infection with antibiotics has resulted in cures of MALT tumors. Furthermore, a recent randomized trial from China demonstrated that early treatment of *H. pylori* with antibiotics can decrease the subsequent incidence of gastric cancer in persons at high risk for that disease.<sup>85</sup>

In some parts of the world, such as the Middle East, a large number of cases of bladder cancer are attributable to chronic schistosomiasis, a parasite.

## OCCUPATIONAL CARCINOGENS

Asbestos induces lung cancer and mesothelioma and is a major cause of cancers of the respiratory tract. Each year in the United States, asbestos is estimated to cause several thousand cancer cases, primarily lung cancer.<sup>8</sup> Asbestos is virtually indestructible and is widely used throughout industrialized environments. Mesothelioma has been reported to develop after a single identifiable exposure to asbestos. In contrast, lung cancer develops chiefly in workers who have been heavily exposed to asbestos, such as asbestos manufacturers, pipe fitters, and shipyard workers. Concerns have also been raised regarding low-level asbestos exposure associated with decaying insulation in older homes and buildings.<sup>86</sup> The carcinogenic effect of asbestos appears to be related to the long, needlelike physical configuration of the fiber. There are concerns that other fibers, such as certain fiberglass insulation materials, might pose a cancer risk.<sup>87</sup> Smoking and exposure to asbestos appear to act synergistically in producing cancer. The combination of smoking and occupational exposure to asbestos increases lung cancer risk about 60-fold.

Bladder cancer has been reported in workers exposed to certain aromatic amines in the dye, rubber, leather, tanning, and organic chemical industries. This has been found to be true for kidney cancers as well.

Other occupational carcinogens include polycyclic aromatic hydrocarbons, such as those found in cigarette smoke. These are also derived from combustion of petroleum and its by-products in diesel engines or in other similar settings.

Certain miners, such as uranium miners, can be exposed to unusual carcinogens such as radon. Radon is inhaled and increases the risk of lung cancer. Studies have shown that there is a dose-response relationship associated with mining and that an interactive effect with cigarette smoking increases the risk of lung cancer in these miners.<sup>88</sup> Other types of miners, such as coal miners, may also have an increased risk of lung cancer.

## CARCINOGENS AFFECTING THE REPRODUCTIVE SYSTEM

Breast cancer is the most common neoplasm in women in the United States and accounts for 28% of all new cancers diagnosed in women in 2010.<sup>1</sup> The cumulative incidence of breast cancer in American women is 9% by 74 years of age. The highest rates worldwide are observed in the industrialized countries of North America and Europe. Rising breast cancer rates in Japan and other newly industrialized nations, as well as in Asian immigrants to the United States, suggest environmental influences.<sup>7,89</sup>

Studies have focused on hormonal factors and the influence of obesity, exercise, diet, and parity in promoting carcinogenesis in the breast and female reproductive organs.<sup>90-95</sup> The risk of breast cancer increases with early menarche, nulliparity, older age at first birth, and late menopause. Available data suggest a slight increase in breast cancer risk with prolonged use of oral contraceptives in women younger than 35 years but not in older women.<sup>90</sup> Prolonged use of postmenopausal hormone replacement therapy has been shown to increase the risk of breast cancer, and the addition of progesterone appears to exacerbate this effect.<sup>91,96</sup> The

Women's Health Initiative (WHI) demonstrated that postmenopausal estrogen use increases breast cancer incidence and mortality.<sup>97</sup> Following reports of increased breast cancer of postmenopausal hormonal use, decreased breast cancer incidence in the United States is attributed to decreased use of postmenopausal hormonal therapy as a result of the WHI results.<sup>98</sup>

In addition, oophorectomy reduces the incidence of breast cancer by about 50%. Taken together, these observations support a unified hypothesis that breast cancer development is promoted by prolonged exposure to cyclic ovarian secretion of estrogens and progesterone. Furthermore, low to moderate alcohol use increases the risk of breast cancer, with a strong association with hormone-sensitive breast cancer.<sup>99,100</sup>

A higher risk of breast cancer has been found in women with benign lesions with histologic evidence of proliferation and atypia. Because most of the known risk factors for breast cancer cannot be modified easily, chemopreventive strategies are being explored for women at high risk for cancer. A large randomized trial has determined that tamoxifen substantially reduces the incidence of breast cancer in women at high risk and reduces the rate of contralateral breast cancer in breast cancer patients.<sup>4</sup> A second trial found that raloxifene can also serve as chemoprevention for breast cancer.<sup>101</sup> Use of conjugated estrogens during menopause appears to retard the progression of osteoporosis and reduce menopausal symptoms.<sup>96</sup> Little is known about environmental causes of carcinoma of the ovary and endometrium. These malignant tumors have some risk factors in common with breast carcinoma, including increased risk with nulliparity and perhaps with obesity and high socioeconomic class.

Multiple primary adenocarcinomas of the breast, ovary, and endometrium have been reported in individuals and in families.<sup>8</sup> The risk of both ovarian and endometrial cancer may be lower in women who have used oral contraceptives. For women who were exposed in utero to diethylstilbestrol, the risk that adenocarcinoma of the vagina will develop in their early adult years is 1 in 1,000. Otherwise, this cancer is extraordinarily rare.<sup>8</sup>

In the past 25 years, age-adjusted incidence rates for prostate cancer in the United States have more than doubled.<sup>1</sup> Prostate cancer is estimated to account for 28% of all incident cancers in males in the United States. Much of the increase in incidence can be explained by the widespread use of prostate-specific antigen (PSA) for early cancer detection.<sup>102</sup> Clinical prostate cancer is much more common in the United States than in Japan. In both countries, however, a large proportion of elderly men have *in situ* malignant changes in the prostate. Prostate cancer incidence and mortality have risen more rapidly in African Americans, whose age-adjusted mortality for prostate cancer is more than double that of whites (56.3 versus 23.6 per 100,000 from 1990 to 1996).<sup>1</sup> Benign prostatic hyperplasia, a common condition in men older than 60 years, does not appear to be strongly associated with prostate cancer risk.

Environmental influences have been examined as an explanation for the rising incidence of prostate cancer and

the higher frequency of advanced prostate cancer in the United States, even in the Asian-American population. Dietary and hormonal influences have been examined in relation to prostate cancer, but their role is still unclear. Evidence suggests that a slightly increased risk of prostate cancer is associated with increased consumption of saturated fat and red meat; vitamins A and D and  $\beta$ -carotene may not decrease the risk.<sup>102</sup>

#### IATROGENIC CAUSES

In more than 50 patients treated with cyclophosphamide for cancer and other serious diseases, bladder cancer developed after cyclophosphamide-induced cystitis.<sup>103</sup> A second drug, phenacetin, is associated with cancer of the renal pelvis and bladder.<sup>104</sup>

Ionizing radiation can induce all major forms of leukemia except chronic lymphocytic leukemia.<sup>8</sup> Studies have provided evidence for and against the association between electromagnetic radiation and risk of leukemia; current evidence tends not to support this association.<sup>105</sup> A high incidence of acute myeloid leukemia has been reported in cancer patients treated with alkylating agents (i.e., melphalan, cyclophosphamide, chlorambucil, and the nitrosoureas), topoisomerase inhibitors, or epipodophyllotoxins.<sup>106</sup> In several large studies, the cumulative leukemia risk at 10 years of follow-up was approximately 5%; the leukemogenic effect of these drugs diminishes with longer follow-up. Clinically, the risk of secondary leukemia needs to be weighed against the benefit of treatment. Alternative nonleukemogenic therapies should be sought; antimetabolites, such as cytarabine, fluorouracil, and methotrexate, do not appear to be carcinogens. Patients who undergo bone marrow transplantation are at higher risk for new solid cancers for at least 10 years after transplantation.<sup>107</sup> The use of granulocyte colony-stimulating factor (G-CSF) is associated with increased risk of acute myeloid leukemia or myelodysplastic syndrome.<sup>108</sup>

#### MISCELLANEOUS ENVIRONMENTAL CAUSES

Ionizing radiation has been recognized as a human carcinogen for a century. This has been a major etiologic factor for cancer following the atomic bomb in Japan, as well as in various occupational settings. Approximately 3 to 5% of all cancers can be attributed to ionizing radiation, including high-dose therapy for cancer and other diseases.<sup>8</sup> Radiation can induce brain tumors, cancers of the skin and thyroid, sarcomas of bone and soft tissue, and cancers of other sites.<sup>11</sup> Cancer of the skin of the scrotum occasionally develops in workers topically exposed to soot and mineral oils. Chemical exposures and viruses have been studied as etiologic agents in brain tumors, Hodgkin disease, and multiple myeloma, but definitive results are scanty. Although several reports have suggested an association between electromagnetic radiation and leukemia and brain cancer, more definitive studies have demonstrated no evidence of an association.<sup>105</sup> Studies have examined the role of herbicides and defoliants, including Agent Orange, which was heavily used during the war in Vietnam. Agent Orange contains dioxins, which are potent animal carcinogens, although no definitive evidence has been found for increased cancer risk in Vietnam War veterans.<sup>109</sup> Excesses of soft tissue sarcoma and NHL have

been reported in workers exposed to dioxins through their manufacture or use in farming for long periods.<sup>8</sup>

### Inherited Factors that Predispose to Cancer

Interest in hereditary influences emerged with the understanding that genetic alterations underlie the process of transformation of a normal cell into a cancer cell. The basis of cancer is the loss of normal genetic control of cellular processes. At the molecular level, cancer is a disorder of genes, particularly oncogenes and tumor suppressor genes. Furthermore, epigenetic control of gene expression is shown to inactivate tumor suppressor genes in various malignancies. Among the estimated 50,000 genes in the human genome, only a small fraction seems to be essential for cancer development. Genetic alterations can alter regulation of cell replication, DNA repair, apoptosis, and immune surveillance against tumor cells. Inherited traits can interact with environmental carcinogens. For example, sunlight increases skin cancers in genetically susceptible Celts and other light-skinned populations. Patients with albinism or xeroderma pigmentosum have a defect in excision repair of ultraviolet light-damaged DNA and develop multiple skin cancers in exposed areas. Epidemiologic studies can help define the influences of both environmental carcinogens and host factors in cancer development.<sup>110</sup>

Hereditary factors in cancer development have been identified in studies of families with a history of cancer. Virtually every form of cancer manifests a tendency to aggregate in families. Close relatives of a cancer patient are at increased risk for the same form of cancer and perhaps other cancers. The excess site-specific cancer risk is usually two to three times above the age- and sex-specific population rate. However, germline (inherited) mutations in some cancer genes can increase the likelihood of cancer development to nearly 100%. These potent cancer genes are rare in the population but serve as important models for studies of carcinogenesis.<sup>111</sup>

#### HIGH-PENETRANCE GENETIC FACTORS

##### *Risk Factors for Retinoblastoma*

A paradigm of hereditary cancers in humans is retinoblastoma. Approximately one third of this childhood cancer occurs in an autosomal dominant pattern with high penetrance. Carriers of a mutated retinoblastoma gene (*Rb-1*) have more than a 10,000-fold excess risk of this eye tumor, as well as a marked increase in the risk of second cancers (sarcomas, melanomas, and brain tumors).<sup>112</sup> The *Rb-1* gene is a tumor suppressor. Loss or inactivation of both alleles of the gene abolishes its tumor suppressor function and leads to tumor development. In hereditary retinoblastoma, one abnormal allele has been inherited from a parent. However, this eye tumor develops only after the second normal allele has been inactivated through a somatic (acquired) mutation or other mechanism. Although inherited mutations in the *Rb-1* gene are rare, somatic mutations in the gene are active in the genesis of many forms of cancer, including carcinomas of the breast, the lung, and other sites. The *Rb-1* protein interacts with the transcription factors and cyclins that regulate progression through the cell cycle. The *Rb-1* gene can also be

inactivated through binding by the transforming proteins of several oncogenic viruses; this protein-protein interaction is one molecular mechanism of viral oncogenesis.

##### *Risk Factors for Familial Neoplasms*

An increasing number of genetic diseases are associated with a high risk of cancer [see Table 2].<sup>111</sup> Neoplasia is the primary manifestation of some cancer genes, such as the *Rb-1* gene. Carriers of these genes can often be identified by a family history of the same cancer in multiple relatives affected at unusually early ages. In other genetic disorders, such as neurofibromatosis, cancer is a less common manifestation of the underlying genetic disease. The finding of a predisposing genetic disorder should alert the physician to the possibility of early diagnosis of associated cancers through periodic surveillance.

##### *Risk Factors for Colorectal Cancer*

Colorectal cancer tends to develop within certain families. In the dominantly inherited disorder adenomatous polyposis coli (APC), colonic polyps arise in adolescence, and the lifetime risk of colon cancer is nearly 100%. The APC tumor suppressor gene was isolated in 1991 and shown to be the inherited mutation in all polyposis families. In contrast, familial colon cancer without multiple polyposis may be caused by germline mutations in one of the DNA repair genes: *MSH2*, *MLH1*, *MSH6*, *PMS1*, or *PMS2*.<sup>113,114</sup> Their phenotypes include familial colorectal cancer and hereditary nonpolyposis colorectal cancer, which accounts for 5 to 10% of these cancers in the United States.<sup>115</sup>

##### *Risk Factors for Reproductive Cancers*

A family history of breast cancer is one of the most consistent risk factors of the neoplasm, particularly in women who have multiple relatives with bilateral premenopausal disease. Hereditary breast cancer accounts for approximately 5% of all breast cancers in the United States. Studies have identified at least five genes predisposing to inherited breast cancer. Clinically, the most important is the *BRCA1* gene, located on chromosome 17q.<sup>116</sup> A second breast cancer gene, *BRCA2*, has been found on chromosome 13q.<sup>117</sup> *BRCA1* and *BRCA2* account for most of the hereditary breast cancers in young women; carriers of *BRCA1* are also predisposed to ovarian cancer of early onset. Women who are carriers of the *BRCA1* mutation have a 50 to 85% probability of developing breast cancer by 70 years of age, and their risk for ovarian cancer is 20 to 50%.<sup>118</sup> Corresponding figures for breast and ovarian cancers associated with inherited *BRCA2* mutations may be lower. The frequency of inherited *BRCA1* and *BRCA2* mutations varies widely among populations; it appears to be higher among Ashkenazi Jews, approximately 2% of whom carry mutations of *BRCA1* or *BRCA2*.<sup>118</sup>

Another susceptibility gene for breast cancer is the *p53* tumor suppressor gene, the inherited defect in most families with dominantly inherited Li-Fraumeni syndrome. The *PTEN* gene, which is associated with Cowden disease, also confers an increased risk of benign and malignant breast tumors, as well as brain, prostate, and thyroid neoplasms.<sup>119</sup> Breast cancer genes might include the ataxia-telangiectasia gene, on chromosome 11q. Ataxia-telangiectasia is a rare

**Table 2 Common Hereditary Cancers and Syndromes Attributable to Germline Mutations in Predisposing Genes**

Gene	Type	Locus	Familial Neoplasms and Syndromes
<i>BRCA1</i>	Tumor suppressor	17q	Hereditary breast and ovarian cancer
<i>BRCA2</i>	Tumor suppressor	13q	Hereditary breast and ovarian cancer
<i>hMSH2</i>	Mismatch repair	2p	Hereditary nonpolyposis colon cancer (also endometrium, brain, urinary tract, other)
<i>hMLH1</i>	Mismatch repair	3p	Hereditary nonpolyposis colon cancer (also endometrium, brain, urinary tract, other)
<i>hPMS1</i>	Mismatch repair	2q	Hereditary nonpolyposis colon cancer (also endometrium, brain, urinary tract, other)
<i>hPMS2</i>	Mismatch repair	7p	Hereditary nonpolyposis colon cancer (also endometrium, brain, urinary tract, other)
<i>NF1</i>	Tumor suppressor	17q	Neurofibromatosis type 1 (neurofibroma, sarcoma)
<i>NF2</i>	Tumor suppressor	22q	Neurofibromatosis type 2 (acoustic neuroma, brain)
<i>RB1</i>	Tumor suppressor	13q	Hereditary retinoblastoma and other second cancers
<i>APC</i>	Tumor suppressor	5q	Adenomatous polyposis coli (colon, brain)
<i>p53</i>	Tumor suppressor	17p	Li-Fraumeni syndrome (sarcoma, breast, brain, leukemia)
<i>MEN1</i>	Tumor suppressor	11q	Multiple endocrine neoplasia type I (pituitary, parathyroid, pancreas)
<i>MEN2A</i>	Oncogene	10q	Multiple endocrine neoplasia type IIA/B (thyroid, parathyroid, pheochromocytoma)
<i>WT1</i>	Tumor suppressor	11p	Hereditary Wilms tumor
<i>VHL</i>	Tumor suppressor	3p	von Hippel-Lindau syndrome (hemangioblastoma, renal cell carcinoma)
<i>TSC1</i>	Tumor suppressor	9q	Tuberous sclerosis 2 (kidney, brain)
<i>TSC2</i>	Tumor suppressor	16p	Tuberous sclerosis 2 (kidney, brain)
<i>CDKN2</i>	Tumor suppressor	9p	Hereditary melanoma
<i>ATM</i>	DNA repair	11q	Ataxia-telangiectasia (breast in heterozygote, lymphoma in homozygote)
<i>PTEN</i>	Tumor suppressor	10q	Cowden disease (breast, thyroid, skin)

autosomal recessive disease in which homozygotes develop neurologic, neoplastic, and other disorders in childhood.

Prostate cancer has a hereditary component, with male relatives of prostate cancer patients exhibiting a twofold increased risk. Hereditary prostate cancer, which accounts for 5 to 10% of all cases, is primarily associated with early-onset disease. Major susceptibility loci for hereditary prostate cancer were recently mapped on chromosome 1 and the X chromosome.<sup>120,121</sup>

#### Other High-Penetrance Genetic Factors

Inherited susceptibility plays a role in other common forms of human cancers, including endocrine and brain tumors, skin cancer, kidney cancer, melanoma, and the hematologic neoplasms. Familial forms of these cancers account for a small fraction of incident cases. Within affected families, however, the inherited cancer gene is an exceptionally potent oncogenic influence that can lead to cancer among multiple relatives.

#### LOW-PENETRANCE GENETIC FACTORS

In addition to highly penetrant cancer susceptibility genes, many low-penetrance genetic variants (polymorphisms) may interact with environmental agents and other genes to modify cancer risk.<sup>19,122</sup> These polymorphisms are associated with only moderate increases in risk, but they can occur at high frequency in the population and contribute to the

development of substantial numbers of cancers.<sup>17,18,20</sup> Unfortunately, the effects of these variants are often small and difficult to measure in heterogeneous populations. For example, rare *HRAS1* alleles in the *H-ras-1* oncogene are reportedly associated with increased breast cancer risk, but new results based on improved analytical methods have failed to support the finding.<sup>122,123</sup> Inconsistent results in studies of low-penetrance cancer genes might also be the result of small sample sizes and misclassification of carcinogenic exposures.<sup>124</sup> Characterization of the role of genetic variants in cancer development can help identify susceptible populations to individualize cancer prevention efforts.

Polymorphisms in genes that encode for proteins involved in metabolism of steroid hormones or carcinogens might alter cancer risks. Variants in the cytochrome P-450 genes are associated with increased risk of lung, esophageal, and head and neck cancers. The genes *GSTM1* and *GSTT1* produce glutathione transferases that are involved in the deactivation of tobacco carcinogens.<sup>17</sup> Certain variants in these genes are associated with an increased risk of bladder cancer and a lower survival rate for patients with lung cancer.<sup>17</sup> A combination of genetic variants in both cytochrome P-450 genes and *GSTM1* may produce gene-gene interactions that further increase cancer risks.<sup>18</sup> Polymorphisms of the *NAT1* and *NAT2* genes may affect susceptibility to cancers of the urinary bladder, colon and rectum, breast, head and neck, and lung.<sup>19,20</sup> Individuals with the slow *NAT1* and

*NAT2* acetylator phenotypes may be prone to bladder cancer, whereas those with fast acetylator phenotypes may be predisposed to colorectal cancer.<sup>20</sup>

Before familial cancers are attributed to genetic susceptibility, chance association and shared exposures to environmental carcinogens should be excluded. Inherited predisposition can be identified through detection of laboratory markers of host susceptibility and by segregation and linkage analysis of the pedigree. With the increasing identification of cancer susceptibility genes, genetic testing of individuals is becoming more widespread. Analysis of the *Rb-1* gene has been used to detect carriers in families with retinoblastoma. In affected families, surveillance of newborns for early cancer can reduce loss of vision. As genes for more common cancers have been found, ethical and social issues have become more complex. Careful consideration must be given to the costs and benefits of genetic testing.<sup>125</sup>

#### EPIGENETICS

The control of gene expression is not simply by alterations in the DNA sequence; it is also controlled through modifications of the DNA sequence and the regulatory proteins. The study of epigenetics initially found that global hypomethylation of DNA was increased in human cancers. More hypermethylated tumor suppressor genes were discovered, as well as the inactivation of microRNA (miRNA) genes by DNA methylation. Both histone deacetylation and DNA methylation have been shown to repress gene expression.<sup>126</sup> Methylation is a marker of an inactive gene, and the methylation of the promoter region of the *MLH1* gene results in colon cancer. *VHL* gene hypermethylation and the development of renal cell carcinoma have also been shown. However, hypomethylating agents, such as azacytidine, do not have significant activity in solid malignancies; they are shown to increase overall survival and progression-free survival in myelodysplastic syndrome.<sup>127</sup>

#### Screening and Early Detection

The recommendations of the American Cancer Society, the National Cancer Institute, and the U.S. Preventive Services Task Force for the prevention and early detection of cancer have received wide attention. These guidelines are intended primarily for asymptomatic patients at average risk for cancer. They do not apply to symptomatic patients, who should be managed by the usual standards of medical practice. Patients considered to be at increased risk because of family history or environmental exposures should seek a physician's recommendations for establishing an appropriate early detection program.

Data are incomplete regarding the costs, risks, and benefits of cancer screening in the general population. A few large randomized studies have been completed for specific cancers, such as breast cancer. These studies have found that periodic mammography reduces breast cancer mortality by 20 to 25% in women 50 to 70 years of age. Data are scanty and uncertain for younger and older women.<sup>128</sup> To be useful, a screening test must detect preclinical cancers that are less likely to be lethal after treatment than if they are allowed to progress to clinical detection. False positive results of

screening tests lead to unnecessary workups and treatment for indolent tumors and increase medical, psychological, and financial costs.<sup>129</sup> The identification of high-risk populations through risk evaluation, including genetic testing, can help channel scarce resources to susceptible persons.

The American Cancer Society has made specific recommendations for the early detection of asymptomatic carcinoma of the colon and rectum, cervix and other pelvic organs, breast, and prostate [see Table 3].<sup>130</sup> However, because of the lack of convincing evidence of benefit from screening for lung cancer, periodic chest x-rays and sputum cytology are not recommended, nor are computed tomographic (CT) scans. Recent results from the National Lung Screening Trial (NLST) from the National Cancer Institute report a 20% reduction in lung cancer mortality for smokers undergoing low-dose CT chest scans versus chest x-rays.<sup>131</sup> This new finding may have an impact on lung cancer screening in coming years. PSA is being increasingly used for prostate cancer detection. Serum PSA levels correlate with the clinical stage of prostate cancer and the volume of the cancer in the gland.<sup>132</sup> Evidence regarding prostate cancer screening with PSA and digital rectal examination is conflicting. The US Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial found no difference in the rate of death, whereas a European study concluded that the rate of death from prostate cancer was reduced by 20%.<sup>133,134</sup> Hence, the National Cancer Institute currently recommends informed decision making between the physician and the patient.

The current screening guidelines can be expected to evolve with the accrual of knowledge and technological advances. For example, the technical quality of mammograms and their interpretation are critical factors in their usefulness. Mammographic detection of cancer is more problematic in the dense breast tissue of younger women, whose tumor growth rates are generally more rapid. After analyzing the same body of evidence from randomized mammographic studies, expert committees have reached different conclusions regarding routine mammographic screening of asymptomatic women 40 to 49 years of age. The American Cancer Society, the National Cancer Institute, and other groups have recommended that women begin receiving annual mammograms once they reach 40 years of age, but the National Institutes of Health consensus panel and the U.S. Preventive Services Task Force did not make this recommendation.<sup>130,135</sup> Of several methods available for colorectal cancer screening, colonoscopy was found to be superior to both double-contrast barium enema and sigmoidoscopy in two studies.<sup>136,137</sup> Of note, CT colonography every 5 years has been added to recommendations from the American Cancer Society.<sup>130</sup> New screening methods, such as magnetic resonance imaging of the breast and spiral CT of the lungs, may further enhance the sensitivity and specificity of screening tests.<sup>138</sup>

Clinicians can help prevent and detect cancer at early stages. They can prevent environmental cancers by counseling patients to avoid tobacco use, asbestos exposure, and unnecessary exposure to ionizing radiation. A brief medical and family history can reveal an unusual predisposition to cancer and a need for closer medical surveillance. In the course of the physical examination, attention to signs of early cancer can lead to curative treatment.

**Table 3 American Cancer Society Recommendations for Early Cancer Detection**

Tissue	Test or Procedure	Sex	Age (yr)	Frequency
Breast	Breast self-examination (BSE)	Female	Early 20s	Should be informed about benefits and limitations and then may choose to do BSE or not
	Breast physical examination	Female	20–39	Every 3 yr
	Mammography	Female	40	Every year
Colorectal*	Fecal occult blood test or fecal immunochemical test or stool DNA test	Male, female	50	Every year
	Flexible sigmoidoscopy	Male, female	50	Every 5 yr
	or Colonoscopy	Male, female	50	Every 10 yr
	or Double-contrast barium enema or CT colonoscopy	Male, female	50	Every 5 yr
Cervix	Papanicolaou smear	Female	Papanicolaou smear and pelvic examination every year for women who are or have been sexually active or have reached 18 yr of age; after three or more consecutive satisfactory normal annual exams, the Pap test may be performed less frequently at the discretion of the physician plus HPV test	
	Pelvic examination		Women > 70 yr with 3 consecutive normal Pap tests may choose to stop	
Endometrium	Endometrial tissue sample	Female	Women at very high risk beginning at 35 yr of age	Should be informed about potential benefits and limitations of screening
Prostate	PSA/DRE DRE	Male	50	Every year Annual PSA/DRE testing should be limited to men with life expectancy of at least 10 yr and men at high risk (those of African descent or with familial risk should initiate testing at 45 yr of age); the benefits and limitations should be discussed with the clinician

Adapted from American Cancer Society. Stay Healthy, Find Cancer Early, Cancer Screening Guidelines. Available at: <http://www.cancer.org> (accessed)

CT = computed tomographic; DRE = digital rectal examination; HPV = human papillomavirus; PSA = prostate-specific antigen.

\*These guidelines are intended for individuals at standard risk. Patients with a family history or other factors that indicate elevated risk should consult their physicians for recommended screening guidelines.

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