Articles

Toward the Primary Prevention of Cancer

BRIAN E. HENDERSON, RONALD K. ROSS, MALCOLM C. PIKE

This is the threshold of an era when many of the most prevalent human cancers can, to a significant extent, be prevented through life-style changes or medical interventions. For lung cancer, the leading cause of cancer deaths in the United States, the major cause, cigarette smoking, is known and strategies for reducing smoking are slowly succeeding. Dietary changes can reduce the risk of developing large bowel cancer, the second most common cancer overall. The etiology of the major cancer in women, cancer of the breast, is sufficiently well understood that large-scale medical intervention trials are imminent. Recent changes in the incidence and mortality of these and the other major human cancers are reviewed with a brief explanation as to why these changes have occurred, followed by a summary of the state of knowledge regarding the major causes of cancer.

CANCER IS NOW THE LEADING CAUSE OF DEATH FOR women in the United States and, if trends continue, will be the overall leading cause of death in the United States by the year 2000. The emerging dominant role for cancer as a cause of mortality is due not so much to continuing increases in cancer mortality but to the remarkable and consistent decline in heart disease mortality over the past four decades. Thus, although the total (age-adjusted) cancer mortality rate has been relatively stable (there was a modest 6% increase between 1950 and 1987), heart disease mortality has fallen to 55% of its rate in 1950 (*1*). The reason for the precipitous decline in heart disease mortality is a combination of a reduced prevalence of major risk factors (such as reduction of smoking, better detection and treatment of hypertension, and a reduction in cholesterol as a result of improved diet) and improved treatment of the various clinical manifestations of cardiovascular disease (*2*). As such, heart disease can serve as a model for the impact of a combination of altered life-style and improved treatment on mortality.

Although there has been little change in overall cancer mortality for at least the last 40 years, there have been major recent changes for some individual cancer types (Table 1). Mortality caused by Hodgkin's disease and cancers of the cervix, uterus (endometrium), stomach, rectum, testis, bladder, thyroid, oral cavity, and pharynx has declined more than 15% (roughly 1% per year) since 1973 (*3*). The decreases in stomach and cervical cancer mortality reflect continuing long-term downward trends. These decreases are believed to be a consequence, respectively, of changes in food preservation practices and consumption patterns (*4*), as well as the early detection and treatment of premalignant and in situ disease (*5*). The decrease in mortality and incidence of endometrial cancer occurred subsequent to a very rapid increase in the incidence of this cancer during the early 1970s. This increase was due primarily to increased use of postmenopausal estrogen replacement therapy (ERT) (*6*). Several factors contributed to the subsequent decline, including a decreased prevalence of use of ERT, changing strategies for prescribing treatment (such as reduced dose and addition of progestogens), and increasing use of oral contraceptives (OCs). The decrease in mortality from testis cancer, in spite of a large increase in incidence, is a result of improved treatment. Similarly, for Hodgkin's disease, the decline in mortality is threefold greater than the decline in incidence. The decreases in mortality from rectal, bladder, thyroid, oral, and pharyngeal cancers also appear to be due primarily to more effective treatment, although treatment advances have not been so well documented or publicized as those for testis cancer and Hodgkin's disease.

Since 1973 increases in mortality (>15%) have occurred for lung cancer, melanoma, non-Hodgkin's lymphoma, and multiple myeloma. Increases in cigarette smoking from 1900 until the early 1960s transformed lung cancer from a rare disease at the turn of the century to the current leading cause of cancer death. The annual (age-adjusted) mortality rate of lung cancer in men has finally leveled off after more than 50 years of unabated increase. In women, lung cancer surpassed breast cancer as the leading cause of cancer death in 1986; rates are expected to continue to increase for at least another 10 years (*7*). The increase in melanoma mortality parallels a larger increase in the incidence of this disease, mainly caused by increased sunburning in fair-skinned populations, attributable to changing fashions and recreational habits (*8*). The increases in mortality from, and incidence of, non-Hodgkin's lymphoma and multiple myeloma remain largely unexplained. Improved diagnostic procedures may be part of the reason for this increase in lymphoproliferative diseases. Immunocytochemistry can distinguish genuine lymphomas from undifferentiated epithelial tumors that have metastasized to lymph nodes from unknown primary sites, and distinguish more definitely extranodal primary lymphomas from cancers of other histologies that occur at the same site. In younger age groups, however, much of the recent increased incidence of certain types of lymphomas can be attributed to the increasing prevalence of human immunodeficiency virus (HIV) infection, which is an established cause of these cancers (*9*).

Earlier detection may explain the substantial increases in prostate and breast cancer incidence, which have occurred without correspondingly large changes in mortality rates. Much of the increase in breast cancer reflects detection of local disease and has accompanied the increased utilization of mammography (*10*). If indeed screening has led to the earlier diagnosis and effective treatment of potentially fatal cancer, then mortality rates should decrease during the next decade. The recent 20% increase in the incidence of brain and other central nervous system (CNS) tumors may be largely explained by the increased availability of x-ray computerized tomography and hence the diagnosis of otherwise "silent" tumors (*11*). Some real increase in CNS tumor incidence may also have occurred as a result of exposure to dental x-rays, especially from the early generations of equipment that resulted in much higher exposure than is experienced today (*12*). The increase in kidney cancer incidence, accom-

The authors are in the Department of Preventive Medicine and the Kenneth Norris, Jr., Comprehensive Cancer Center, University of Southern California School of Medicine, 1441 Eastlake Avenue, Los Angeles, CA 90033.

Table 1. Cancer sites ranked by percentage change in mortality and incidence between 1973 and 1987. (This is based on rates per 100,000 age-adjusted to the 1970 U.S. standard population.) Table 1 was adapted from Ries *et al.* (*3*).

Cancer site or type	Percentage change, 1973–1987	
	Mortality	Incidence
Greater than 15% decrease in mortality and incidence		
Hodgkin's disease	−49.5	−15.9
Cervix	−39.6	−36.4
Stomach	−29.4	−20.5
Uterus (endometrium)	−19.8	−26.1
Greater than 15% decrease in mortality but stable or increasing incidence		
Testis	−60.0	39.0
Rectum	−39.9	−3.3
Bladder	−22.7	12.3
Thyroid	−20.6	14.6
Oral cavity and pharynx	−16.2	−1.3
Greater than 15% increase in mortality with increasing incidence		
Lung	34.1	31.5
Melanoma	29.8	83.3
Multiple myeloma	23.6	10.5
Non-Hodgkin's lymphoma	21.7	50.9
Greater than 15% increase in incidence with smaller change in mortality		
Kidney	12.9	27.0
Brain and other nervous system	9.4	23.0
Prostate	7.2	45.9
Breast	2.2	24.2
Fairly stable mortality and incidence		
Esophagus	11.3	12.3
Ovary	−6.4	−6.8
Larynx	−6.0	0.5
Leukemia	−5.6	−10.2
Liver	−4.7	14.5
Pancreas	−2.0	−5.6
Colon	−1.6	10.4
All sites	5.4	14.6

panied by a somewhat lesser increase in mortality, is at least in part a consequence of cigarette smoking (*13*).

Changes in mortality and incidence since 1973 for six of the remaining seven cancer sites in Table 1 are relatively small. With the exception of cancer of the esophagus, the mortality rates show small decreases. The incidence of esophagus and liver cancer have increased by 12.3 and 14.5%, respectively, probably because of the combined effects of tobacco and alcohol.

The Causes of Cancer

The International Agency for Research on Cancer (IARC) and other cancer research organizations periodically publish lists of human carcinogens. These lists typically focus on individual chemicals for which epidemiologic evidence to support a carcinogenic potential is accompanied by sufficient experimental evidence to establish causation beyond a reasonable doubt (*6*). In this article we have chosen to use a broader definition of "cause," based not on individual chemicals but on categories of human environmental exposures, for which epidemiologic evidence alone is sufficiently consistent and strong to categorize these as causes of cancer (Table 2). This definition allows us to include exposures to cigarettes and dietary animal fat, which clearly alter cancer risk even though the precise chemical constituents and the mechanism for the increased risk have not been definitively established. In general, the exposure categories listed cause cancer either by direct genotoxic effects on DNA (for example, radiation) or by increasing cell proliferation (for example, hormones) or by a combination of both effects (for example, tobacco).

The increased cell proliferation mechanism actually appears to be the most important (*14–16*). Molecular genetics has provided evidence that cell division is essential for the genesis of human cancer and that an increased rate of cell division will increase cancer risk. "Increased" may imply mitotic activity above the baseline rate or division of a subset of cells that would ordinarily not be dividing. Cell division increases the risk of genetic errors of various kinds. Adducts or other single-stranded DNA damage may be converted to gaps or mutations, and mitotic recombination (such as nondisjunction or gene conversion) may result in more profound changes than those from a single mutation. The development of a fully malignant tumor appears to involve multiple stages—the activation or altered expression of proto-oncogenes to oncogenes and the loss or inactivation of tumor suppressor genes, which control normal cellular activity. The activation of proto-oncogenes, whether by mutation, translocation, or amplification, requires cell division. Inactivation of a tumor suppressor gene appears to involve first a mutational event that inactivates one allele, followed by a deletion during mitosis that results in homozygosity. Both the fixation of the initial mutagenic event and the loss of the wild-type allele of the tumor suppressor gene require cell division. The same agent causing cell proliferation (for example, a hormone) can act at all stages in the pathogenesis of a malignant phenotype. Removal of the causative agent at any stage (except possibly very late) can prevent or delay full development of the cancer.

Chemical and physical carcinogens leave traces of their activities on DNA because of the specific patterns of base changes they induce. We may be able to use knowledge of the mutation patterns of genes believed to be involved in human cancer to predict the likelihood that an exogenous DNA-damaging agent may be involved. It may ultimately be possible to predict what the agent might be. For example, liver mutations typically are found at one nucleotide pair of codon 249 of the tumor suppressor gene p53 in liver cancers occurring in individuals who live in geographic areas where exposure to both aflatoxin and hepatitis B virus (representing a probable and an established cause of liver cancer, respectively) are common (*17*).

Tobacco

Tobacco, alone or in combination with alcohol, remains the most important cause of cancer, accounting for about one of every three cancer cases occurring in the United States today (*18*). Nearly all tobacco-related cancer is due to active smoking or to direct exposure to other tobacco products. However, evidence is strong that passive smoking, in which nonsmokers are exposed to sidestream smoke from burning tobacco and from mainstream smoke exhaled by smokers, is also associated with a modest increased risk of lung cancer and perhaps other cancers (*19*), although the overall contribution of passive smoking to tobacco-related cancer occurrence is small. Cigarettes are far and away the most important cause of tobacco-related cancer, but other forms of tobacco are also established carcinogens. Smokeless tobacco (chewing tobacco and snuff), which is known to cause cancer of the oral cavity, is particularly noteworthy. There were an estimated 12 million users of smokeless tobacco in the United States in 1985; a substantial proportion of these users were adolescents.

If smoking is stopped late in life, even after heavy long-term smoking, subsequent cancer risk will be greatly reduced relative to the risk had smoking been continued. However, the cancer risk of ex-smokers remains elevated relative to the risk of a lifetime

nonsmoker. This effect combined with continued smoking by a sizable minority of the population means that, despite the success of smoking prevention and cessation programs, cancers associated with tobacco will remain a major public health problem for decades. Ominously, in many populous developing countries current tobacco consumption has surpassed even the highest levels achieved in the United States, and the eventual toll in morbidity and mortality in these countries will be staggering (*20*). In light of these realities, it is imperative that researchers explore other countermeasures. Lower tar cigarettes are associated with lower cancer risks than cigarettes of high-tar content, but regular smokers of low-tar cigarettes still have a much higher cancer risk than nonsmokers (*18*).

The possible anticarcinogenic activity of various micronutrients has been extensively studied in relation to lung cancer. A consistent moderate decrease in risk of lung cancer has been observed with increasing consumption of one such micronutrient, β-carotene, in studies in the United States and Europe (*21*), and, although data are less extensive, increasing intake of β-carotene has also been linked to decreased risk of other epithelial cancers. Moreover, prospective studies have consistently found that patients who develop cancer, especially lung cancer or other smoking-related cancers, have lower levels of serum β-carotene than healthy controls (*22*). Although smokers consume less β-carotene than nonsmokers and there has been inadequate adjustment for smoking in some of these published studies (*23*), the evidence appears strong that β-carotene can reduce the incidence of lung cancer. Studies in Asia, however, are less consistent (*24*), and further work on this subject is warranted. β-Carotene is a member of a class of micronutrients, the carotenoids. The characterization of these in common fruits and vegetables will soon be available from the Department of Agriculture. This will enable studies to be undertaken to identify whether other carotenoids may provide protection against lung and other cancers.

Much less data are available on the relation between lung cancer risk and other micronutrients such as vitamin C and vitamin E which, like β-carotene, can serve as antioxidants. At present, the data on these other compounds also suggest a protective effect.

Among cancers caused by smoking, lung cancer is by far the most important. Tobacco, however, contributes to mortality from many other cancers, including those of the oral cavity, esophagus, larynx, pancreas, and bladder. There are populations characterized by relatively high smoking levels, yet low mortality rates of one or several of the smoking-related cancers. For example, U.S. blacks and New Zealand Polynesians have very high smoking rates and substantial lung cancer rates, but relatively low bladder cancer rates (*25*). Such observations have focused attention on determinants of individual susceptibility to cancer among smokers. Genetically determined metabolism of smoking-related carcinogens may affect individual risk. Acetyltransferase is an enzyme system responsible for the metabolism of aromatic amines, a class of chemicals present in cigarette smoke and known to cause bladder cancer. This enzyme is genetically regulated and individuals can be characterized as slow or rapid acetylators, depending on whether they are homozygous for an autosomal recessive gene. There is some evidence that "slow acetylators" are at increased risk of bladder cancer (*26*).

An isoenzyme of a cytochrome P-450 may be linked to lung cancer risk (*27*). One can test for this isoenzyme by measuring the rate of metabolism of debrisoquine, an antihypertensive drug. Extensive research is now under way to further analyze this and other possible genetic linkages to lung cancer susceptibility.

Table 2. Estimated number of new cancer cases in the United States in the year 1990 by site and major cause or causes.

Cancer site	Number*	Percentage	Major cause or causes	
			Known or probable	Possible
Lung	157,000	15	Tobacco	
Colon and rectum	155,000	15	Animal fat, low fiber	Alcohol, sedentary life-style
Breast	150,900	15	Ovarian hormones	
Prostate	106,000	10	Testosterone	Estrogen
Bladder	49,000	5	Tobacco	
Non-Hodgkin's lymphoma	35,600	3	(HIV, HTLV-I)†	
Uterus (endometrium)	33,000	3	Estrogen	
Oral cavity and pharynx	30,500	3	Tobacco, alcohol	
Pancreas	28,100	3	Tobacco	
Leukemia	27,800	3	X-rays	
Melanoma	27,600	3	Ultraviolet light (sunburning)	
Kidney	24,000	2	Tobacco	Analgesics, diuretics
Stomach	23,200	2	Salt, tobacco	*Helicobacter pylori*
Ovary	20,500	2	Ovulation	
Brain and other nervous system	15,600	2	Trauma, x-rays‡	
Cervix	13,500	1		Papillomaviruses
Liver	13,100	1	Hepatitis viruses, alcohol	Tobacco§
Larynx	12,300	1	Tobacco, alcohol	
Thyroid	12,100	1		Iodine excess
Multiple myeloma	11,800	1		
Esophagus	10,600	1	Alcohol, tobacco	
Hodgkin's disease	7,400	<1		
Testis	5,900	<1		In utero estrogen
All other sites‖	69,500	7	Multiple factors	
Total	1,040,000	100		

*From Ries *et al.* (*3*). Projections for 1990 were obtained for the American Cancer Society based on the incidence of cancer for 1984–1986 applied to the 1990 estimated total U.S. population. †Although HIV is an increasingly important cause of non-Hodgkin's lymphoma, it nonetheless currently accounts for only a small proportion of cases. HTLV-I refers to human T cell lymphotrophic virus. ‡Trauma and x-rays are causes of meningiomas and acoustic neuromas, which constitute about 35% of all brain and other nervous system tumors (*16*). The cause or causes of the other types of brain tumors,mainly gliomas, are unknown. §Aflatoxin contamination of nuts and grains may constitute a major cause of liver cancer worldwide but is unimportant in the United States (*6*). ‖The number of new cases of Kaposi's sarcoma has been increasing as a sequelae of HIV infection. These nonepithelial cancers of the skin were not separately estimated in this report. However, the actual number of cases in 1990 may exceed the number of testis cancer cases (*9*).

Diet

There is substantial agreement that the major cancers of the gastrointestinal tract—stomach, colon, and rectum—are causally related to certain dietary factors. These cancers accounted for approximately 17% of all new cancers in the United States in 1990. Cancer of the nasopharynx is another cancer that has been clearly linked to dietary factors, namely, salted fish and similar preserved foods commonly eaten by high-risk southern Chinese populations (*28*). However, this cancer is uncommon in the United States.

The decline in stomach cancer incidence that has occurred throughout the world has paralleled a decline in the use of salting and pickling for preserving food and a concomitant increase in the consumption of fresh fruits and vegetables. International mortality rates from stomach cancer correlate well with mean ratios of urinary sodium to creatinine (an index of sodium intake). A direct relation between consumption of preserved or salty foods and stomach cancer has been consistently observed in case-control and correlational studies conducted in various high- and low-risk populations (*29*). The corrosive effect of a high-salt diet on stomach mucosa leading to cell injury, death, and regeneration may partially explain this association (*16*). Consumption of fresh fruits and vegetables has consistently been found to decrease the risk of stomach cancer.

Epidemiological evidence from case-control studies suggests a relation between fat from red meats ("animal fat") and colorectal cancer (*30, 31*). An individual's consumption of total fat, saturated fat, and animal fat are, however, highly correlated so that the epidemiological studies are not completely consistent in the kind of fat intake that is most closely associated with cancer. The data, however, point consistently to animal fat as a risk factor, and results of cohort studies support this association. The Nurse's Health Study (*30*) and the Adventist Health Study (*31*), both of which used a food frequency questionnaire to assess fat consumption, found a significant association between animal fat consumption and colon cancer risk (Table 3). In these epidemiologic studies, the association between colon cancer risk and the consumption of fat from dairy products was generally weaker than that with the consumption of fat from beef, lamb, and pork.

These results suggest a 50% decrease in consumption of animal fat would result in about the same reduction in colon cancer risk. In rodents, diets high in saturated fat induce inflammation and superficial lysis of the colonic epithelium followed by compensatory regeneration of lost cells. This stimulatory effect on colonic epithelial cell division has been suggested as a mechanism for the role of saturated fat in the pathogenesis of colon cancer (*16, 42*).

Considerable epidemiological data support the hypothesis that a diet low in fiber is associated with an increased risk of cancer of the colon (*43*). Although there is general consistency among studies in establishing this relation, the strengths of the observed associations vary considerably, as does the source of the protective effect of fiber (vegetables, fruits, or cereals). In the Nurses Health Study (*30*), women with the highest animal-fat intake and the lowest crude-fiber intake had the highest risk of colon cancer. There is a credible biological basis for this association, as dietary fiber decreases transit time through the colon and increases the water content in the intestinal lumen, thus diluting other nutrients, such as animal fat. A growing consensus from several governmental agencies suggests an intake of fiber of 20 to 30 g per day, roughly double the average intake in the U.S. diet (*44*). Increasing fiber intake to this level, in conjunction with a reduction in animal fat intake as described above, should further reduce colon cancer risk.

The relation between individual dietary constituents, particularly fat, and the hormone-related cancers (breast, endometrium, ovary, and prostate) is unclear. Excess total calorie intake compared to energy output leads to obesity, an important risk factor for cancer of the endometrium. A similar intake of excess calories over expenditures during childhood predisposes children to an earlier puberty, an important risk factor for breast cancer. Total caloric intake rather than the composition of that intake seems to be the essence of the relation between diet and these cancers (*15*).

Prentice and Sheppard (*45*) have used the international variations in diet and cancer incidence to argue that fat consumption is as strongly related to breast, prostatic, ovarian, and endometrial cancers as it is to colon and rectal cancer. However, the results of case-control and cohort studies have produced, at best, inconsistent results. Among three cohort studies that have used food-frequency questionnaires to study the relation of diet and breast cancer, there has been no consistent relation observed with either total fat, saturated fat, or vegetable fat (Table 3). Results from the Canadian National Breast Screening Study (*34*) showed evidence of a positive association between breast cancer and total fat intake, but this conclusion was based on a small elevation in risk in the highest quartile of dietary fat consumption, and there was no evidence of a dose-response relation.

It is difficult to refute a postulated association between polyunsaturated fat and breast and prostate cancer, as it is more difficult to quantitate consumption of these fats than animal fats accurately by means of a food-frequency questionnaire. Misclassification of intake may mask a real association (*45, 46*). Only the Nurses Health Study and the Canadian National Breast Screening Study have published data on polyunsaturated fats (of which linoleic acid is the most common), and the results are not consistent. Future dietary studies may help to resolve this issue, but it may be more fruitful to study the relation between changes in intake of various dietary fats to

Table 3. Results from prospective studies of diet (*30–36*) as assessed by a food frequency questionnaire for cancers of the breast, prostate, and colon. AHS, Adventist Health Study; NHS1, Nurses Health Study 1; CBSS, Canadian National Breast Screening Study; LCS, Lutheran Brotherhood Cohort Study. Those cohort studies utilizing limited food frequency questionnaires or 24-hour recall diet only and those with small sample sizes are not included [Stemmerman *et al.* (*37*), Garland *et al.* (*38*), Hiryama (*39*), Jones *et al.* (*40*), Severson *et al.* (*41*)].

Study	Total cases	Nutrient	Relative risk across exposure categories				
			Lowest	Intermediate			Highest
		Colon cancer					
NHSI (*30*)	150	Total fat	1.00	2.48	1.88	2.61	2.00††
		Animal fat	1.00	1.22	1.27	1.55	1.89**
		Saturated fat	1.00	1.09	1.28	1.81	1.39††
		Vegetable fat	1.00	1.04	0.94	1.13	0.92
AHS (*31*)	141	Animal fat	1.00		1.55		1.80††
		Breast cancer					
NHS1 (*32*)	601	Total fat	1.00	0.80	0.88	0.81	0.80
		Saturated fat	1.00	0.80	0.91	0.77	0.84
		Linoleic acid*	1.00	0.84	0.75	0.86	0.88
AHS (*33*)	215	Animal fat	1.00		0.95	1.19	1.21
		Total fat	1.00	0.80	0.88	0.80	0.82
CBSS (*34*)	519	Total fat	1.00		0.73	0.98	1.30
		Saturated fat	1.00		0.76	0.97	1.08
		Polyunsaturated fat	1.00		0.82	1.09	1.23
		Monounsaturated fat	1.00		1.09	1.06	1.30
		Prostate cancer					
AHS (*35*)	180	Animal fat	1.00		0.84	0.98	1.35
LBCS (*36*)	149	Meat	1.00		0.9	1.1	0.8
		Dairy products	1.00		1.2	0.8	1.0

*Comparable "weak" inverse trends observed for monounsaturated fat and total polyunsaturated fat (data not shown). **$P = 0.01$. ††$P = 0.05$.

ovarian steroid hormone levels, which are known to be related to rates of cell division in breast tissue.

Alcohol consumption has independent effects [as well as multiplicative (synergistic) effects with tobacco] in increasing risk of cancers of the oral cavity, pharynx, larynx, liver, and esophagus (*47*). Spirits, beer, and wine seem to produce an equivalent effect on cancer risk (*48*). Alcohol consumption has been consistently linked to colorectal cancer and female breast cancer. Alcohol stimulates rectal cell proliferation in the rat (*49*), providing a possible mechanism for the observed association with large bowel cancer. No clear mechanism has been elucidated for the association between alcohol and breast cancer, leaving the etiologic significance of this relation in doubt (*50*).

There is considerable but not yet conclusive evidence from case-control studies that vitamin C has a protective effect against several epithelial cancers, especially cancers of the esophagus, larynx, and oral cavity (*51*). The possible role of such micronutrients in cancer prevention is an area of intense research effort. Several clinical trials have been mounted to test the hypothesis that ingestion of compounds such as β-carotene, vitamin E, and vitamin C that trap oxygen free radicals may lower cancer risk in patients at elevated risk of cancers of the lung, esophagus, colon, and skin. One such trial of skin cancer prevention has been reported, and, although enough β-carotene was administered to raise plasma levels more than eightfold, no difference was found in skin cancer occurrence rates after 5 years (*52*); however, skin cancer had not been found to be associated with low β-carotene intake, so this result should not be overinterpreted.

Hormones

Hormones are associated with another group of cancers that comprised almost one-third of the new cancer cases in 1990 (*15, 53*). Endometrial cancer is caused by cumulative exposure to estrogens in the absence of progestogens (progesterone or its synthetic analogs). Breast cancer is also related to cumulative exposure to estrogens, an effect enhanced by progesterone (*54*). Ovarian cancer is related to ovulation, which is a direct result of more complex hormonal changes. Prostate cancer is most likely related to cumulative exposure to testosterone or its metabolic derivative dihydrotestosterone, perhaps in combination with estrogen, but the epidemiologic evidence for this is sparse. In utero exposure to exogenous and possibly endogenous estrogens appears to increase the risk of both testicular and ovarian germ-cell tumors, but the epidemiologic evidence is again scanty (*15, 53*).

Endometrial cells divide in response to estrogen, but the simultaneous presence of progestogens can reduce or even eliminate such mitotic activity. Events that create estrogen stimulation "unopposed" by progestogen increase endometrial cancer risk, whereas events that decrease unopposed estrogen exposure decrease risk (*15, 53, 55*).

Use of combination-type OCs, which involve daily doses of estrogen and progestogen for 21 days followed by 7 days with no treatment, reduces cancer risk because the endometrium is exposed to unopposed estrogen only during the 7 days when no hormones are taken, and the serum level of estrogen is very low during this time (*56*). Increasing parity decreases risk because the high estrogen levels during pregnancy are consistently opposed by very high progesterone levels. Obesity increases endometrial cancer risk in premenopausal women because of the associated anovulation and thus progesterone deficiency, with estrogen levels remaining sufficiently high to cause maximal stimulation of endometrial cells. Obesity further increases risk in postmenopausal women because of the associated increase in unopposed estrogen production by adipose tissue (*55*). The marked increase in endometrial cancer risk with increasing duration of use of ERT (approximately a threefold increase relative to that of nonusers for each 5 years of treatment) is further evidence that estrogen-induced proliferation of endometrial tissue increases the risk of this disease.

Breast cells proliferate in response to estrogens; the simultaneous presence of progesterone appears to further increase the rate of such cell division (*15, 16, 53*). The clearest demonstration that increased levels of these two hormones, in combination, increase breast cancer risk is that early menarche and late menopause are such important risk factors for this disease (*54*). Breast cancer risk is reduced 10 to 20% each year menarche is delayed. Moreover, for any given age at menarche, rapid establishment of regular menstrual cycles, with the associated increased hormone levels, further enhances risk. Women who stop menstruating before age 45, either naturally or through surgical intervention, have half the risk of breast cancer of women who continue to menstruate to age 55 or beyond. The association of obesity with a decrease in breast cancer in premenopausal women can be attributed to the increase in anovulatory cycles and thus a decrease in absolute levels of estrogen and progesterone. After menopause, obese women have an increased breast cancer risk; this is due to their higher serum estrogen levels.

OCs induce levels of breast cell division similar to those that occur in the normal menstrual cycle; the reduced production of ovarian steroids caused by OC use is compensated for by the synthetic estrogen and progestogen in the OC itself (*54*). OC use is thus not generally associated with either an increase or a decrease in breast cancer risk, although OC use early and late in reproductive life when anovulatory cycles are common may increase risk because the hormonal exposure to breast tissue from the OC is greater than would be normally occurring (*56*).

Long-term use of postmenopausal ERT results in a modest increase in breast cancer risk (approximately a 10% increase relative to nonusers for each 5 years of therapy), in line with predictions based on the serum estrogen levels associated with such exposure (*54*). In the only relevant study so far published, a distinctly larger increase in breast cancer was found among women who had used a progestogen along with ERT than among women who used estrogen alone. Although the magnitude of the increase in risk was surprising, this observation is consistent with the increased mitotic activity of breast cells during the luteal (postovulation) phase of the menstrual cycle when progesterone levels are high (*57*).

Women with breast cancer have higher estrogen levels than healthy control women, and estrogen levels are higher in populations characterized by high breast cancer rates. In fact, differences in premenopausal steroid hormone levels, when considered in conjunction with population differences in average age at menarche and weight, are sufficient to explain the four- to sixfold greater breast cancer incidence in the United States than in Japan (*58*).

Pregnancy is associated with very high levels of estrogen and progesterone and might be expected to increase breast cancer risk. In fact, the relation between pregnancy and breast cancer risk is complex. The high hormone levels during pregnancy induce cell differentiation, as well as cell proliferation. The effect on breast cancer risk is a short-term increase in risk followed by a long-term decrease. Recent observations in populations characterized by frequent and long-term breast feeding support a substantial protective effect of lactation, probably related at least in part to the associated anovulation (*15, 53*).

Ovarian cancer appears to develop from the epithelial cells on the surface of the ovary. The primary stimulus for division of these cells is ovulation. After each ovulation, these cells replicate to cover the exposed surface of the ovary. Those factors that prevent ovulation help protect against the development of ovarian cancer (*59*). Com-

plete and incomplete pregnancies and OC use all reduce the risk of ovarian cancer. The degree of protection from all three factors is clearly related to the duration of their associated periods of anovulation; however, the effect of pregnancies appears to be greater than what can be explained on the basis of anovulation alone (*59*).

Testosterone, after conversion to dihydrotestosterone by the enzyme 5α-reductase, controls mitotic activity in the prostate. In dogs, the only animal other than human males with a reasonably high incidence of prostatic carcinoma, estrogens enhance the effect of androgens on prostate growth by increasing androgen-receptor content. The quantitative relation between testosterone and estrogen levels in human males, the rate of cell proliferation in the prostate, and prostate cancer risk has not been, however, well studied. Epidemiologic data to support such a testosterone plus estrogen relation in human males are sparse, at least partly because no definitive and reproducible markers of hormonal events exist in human males. Few experimental strategies exist for inducing adenocarcinomas of the prostate (*60*). Noble demonstrated that exogenous administration of testosterone could induce prostatic adenocarcinomas in rats and sequential administration of an estrogen could further increase the tumor yield (*61*). Bosland has induced prostatic adenocarcinomas in rats with the chemical carcinogen *N*-methyl-*N*-nitrosourea, but hormonal priming with testosterone to stimulate maximal cell proliferation was required for tumor induction (*62*). All known models of prostatic adenocarcinoma require an androgen.

Black Americans have the highest rate of prostate cancer in the world, whereas Japanese have among the lowest (*25*). These differences in risk are set early in life, as these risk differentials are already present for men in their 40s, when prostate cancers first appear. Serum testosterone and estrogen levels in young black men are sufficiently higher than in young white men, to account for their approximately twofold greater incidence of prostate cancer later in life (*63*). Black women have markedly higher serum levels of testosterone and estradiol (the biologically most potent estrogen fraction) during early pregnancy than do white women, averaging nearly 50 and 40% higher, respectively (*64*). It seems plausible these high levels in utero may contribute to the very high prostate cancer rates observed in black men by determining end organ androgen production or sensitivity, for example. The reasons for the high testosterone and estrogen levels in the black population are not known. The low rates of prostate cancer in Japanese may be due to differences in intra- or extraglandular androgen metabolism, but there are few data available on this possibility.

Age at menarche is related to the balance between energy intake and expenditure during late childhood and early adolescence. Regular exercise may delay the onset of regular ovulatory cycles (*65*). Both factors, delay in menarche and delay in onset of regular cycles, will have an important protective effect on breast cancer, and probably on endometrial and ovarian cancer. Avoidance of obesity and moderate physical activity beginning in childhood should be encouraged. Not only will risk of several hormone-related cancers be reduced but reduction in cardiovascular disease risk will be an additional important health benefit. Moreover, moderate physical activity is associated with reduced risk of colon cancer (*66*). Physical activity promotes progressive waves of bowel contraction, decreasing transit time and, like fiber, decreasing colonic mucosal exposure to animal fat.

In addition to these life-style changes, the use of antagonists can reduce the risk of hormone-related cancers. The antiestrogenic drug tamoxifen has been widely promoted in trials for primary chemoprevention of breast cancer (*67*). Several families of drugs that block testosterone activity in the prostate gland have recently been developed as possible chemopreventive agents for prostate cancer. The widespread use of OCs has already had an effect on the incidence of ovarian and endometrial cancer (*68*). In women who have used OCs 5 years, endometrial cancer risk is reduced about 55% relative to that of nonusers; whereas ovarian cancer risk is reduced about 40%. An alternative form of contraception has been proposed that would utilize a gonadotropin-releasing hormone agonist to totally, but reversibly, eliminate ovarian steroid function (*69*). By combining a gonadotropin-releasing hormone agonist with a very low-dose estrogen and progestogen regimen, it is projected breast cancer risk could be reduced by 50% after 10 years (*69*) and the protective effect against ovarian cancer would be the same as that of OCs.

Other Causes of Cancer

Finally, there is a group of cancers, accounting for about 20% of the total cancer burden, that are known or thought to be caused by a variety of potentially preventable extraneous factors including viruses, drugs, exposure to medical and dental x-rays, exposure to ultraviolet light, and chronic irritation or trauma.

Iatrogenic intervention, by prescription of drugs including chemotherapeutic agents, or by administration of diagnostic or therapeutic radiation, can alter risk of cancer. Although iatrogenic causes of cancer, even when considered as a group, represent a relatively small contribution to the overall cancer burden, they are important, particularly as they are potentially preventable.

As described above, use of ERT increases risk of both endometrial and breast cancers, whereas iatrogenic intervention through use of OCs reduces endometrial and ovarian cancer risk. OCs increase the risk of liver cancer in young women (*70*), but such tumors are uncommon. Other commonly used prescription and over-the-counter medications may also increase cancer risk. In utero exposure to the synthetic estrogen diethylstilbestrol is associated with adolescent and young-adult adenocarcinomas of the vagina in female offspring (*71*). Phenacetin is an established carcinogen to the lower urinary tract (*6*). Although phenacetin is no longer part of the formulation of any over-the-counter analgesics sold in the United States, acetominophen-containing compounds remain widely used for treating a variety of specific and nonspecific conditions. Acetominophen is the major active metabolite of phenacetin and has been shown to transform cultured cells. Aspirin is a potent nephrotoxin but appears to be nonmutagenic (*72*). Both aspirin use and acetominophen use have been associated with risk of cancer of the renal pelvis (*72*). Diuretics have been linked recently to renal cell carcinoma (*13*). Whether long-term use of analgesics or diuretics increases mitotic activity in the kidney remains to be determined.

Ionizing radiation can cause leukemias and many solid tumors (for example, thyroid, breast, and salivary gland). These relations have been established for the most part in cohorts of individuals exposed to relatively high radiation doses, such as atomic bomb survivors or those undergoing radiation treatment for specific health problems (*6*). In the United States, 80% of exposure to man-made sources of ionizing radiation comes from medical x-rays. The relation between low-dose diagnostic radiation and cancer remains controversial, in large part because of the complex methodological issues involved in studying this relation. Nonetheless, there exist compelling data that diagnostic x-rays to the trunk are related to risk of chronic myelogenous leukemia and that the level of risk increases with increasing x-ray dose to active bone marrow (*73*). Preliminary data suggest a similar relation with acute myelogenous leukemia, but with a shorter latency interval between exposure and diagnosis. At least 16% of all leukemias in the United States are caused by diagnostic radiation (*74*), it is estimated.

There are numerous examples of clearly established associations of

specific tumors with physical or mechanical irritation or trauma. Perhaps the strongest among these is the relation of gallbladder cancer to a history of gallstones. Gallstones are present in some 80% of patients with gallbladder cancer. Head trauma can lead to the development of intracranial meningiomas (*16*). Asbestos fibers lodged in the lung can induce lung cancer or mesothelioma (*6, 16*). In each of these examples, the most likely mechanism involves tissue damage induced by the trauma (gallstones abrading the gallbladder wall, injury to the meninges from head trauma, or asbestos fibers lodging in the mesothelium and causing cell injury and irritation), followed by cell proliferation during the repair process (*16*).

The great difficulties in establishing a causal relation between a putative cancer virus and a human cancer have recently been summarized (*75*). The strongest evidence for a direct cause-and-effect relation is between hepatitis B virus and hepatocellular carcinoma. The prospective study by Beasley *et al.* (*76*) is so strongly suggestive of a causal association that large-scale vaccine prevention trials are now under way. There is also very strong epidemiologic evidence to support a causal relation between human T cell lymphotropic virus type 1 and certain T cell lymphomas. Epstein-Barr virus appears to be an "opportunistic" viral carcinogen, which, in conjunction with a congenital or acquired immunodeficiency state, such as is induced by chronic malaria or HIV, is effective in causing Burkitt and other high-grade lymphomas. There is evidence that human papillomavirus is causally related to cervical cancer. These and other possible human carcinogenic viruses are discussed at length in the review by zur Hausen (*77*) and will not be further reviewed here. Other types of microorganisms may play a role in human carcinogenesis. *Helicobacter pylori* infection is a major cause of chronic gastritis in some parts of the world (*78*). Infection with this bacterium has recently been implicated in stomach cancer etiology, possibly through the same mechanism as described above for salt—that is, cell injury and death followed by cell division as part of the repair process (*79*).

Occupational exposures to specific carcinogenic agents are not likely to account for more than 4% of cancers in the United States. The actual percentage may be substantially lower (*18*). The single most important known occupational carcinogen is asbestos. The increase in asbestos-related lung cancer and mesothelioma seems to have peaked during the mid-to-late 1980s as a much-delayed result of extensive occupational exposure of workers, especially in shipyards, to asbestos during World War II (*80*).

Conclusions

We now have sufficient knowledge to move energetically toward the prevention of a significant proportion of human cancer. The majority of the causes of cancer (such as tobacco, alcohol, animal fat, obesity, ultraviolet light) are associated with life-style; that is, with personal choices and not with the environment in general. The widespread public perception that environmental pollution is a major cancer hazard is incorrect.

For the hormone-related cancers, attempts to modulate the relevant hormone effect should be pursued. A better understanding of the determinants of adult hormone levels is necessary before primary prevention of these cancers is feasible through alteration in life-style.

It is imperative health professionals continue to monitor iatrogenic exposures that are potentially carcinogenic. Undoubtedly, additional etiological associations will be identified as the number of available pharmaceuticals and the degree of diagnostic x-ray exposure grows.

Finally, there are some cancers for which vaccine prevention holds promise. The current attempts to implement a hepatitis B vaccination program on a wide scale to control liver cancer in high-risk areas of Africa and Asia is a major public health undertaking. HIV-associated lymphomas and Kaposi's sarcoma will be a growing cancer epidemic for the next several years that can clearly be mitigated by an effective HIV vaccine.

REFERENCES AND NOTES

1. National Center for Health Statistics, *Health, United States, 1984* [Department of Health and Human Services (DHHS) Publication (PHS) 85-1232, Public Health Service, Washington, DC, 1984]; National Center for Health Statistics, *Vital Statistics of the United States, 1987*, vol. 2, *Mortality*, Part A [DHHS Publication (PHS) 90-1101, Public Health Service, Washington, DC, 1990]. This review focuses on cancer in the United States. Patterns of cancer similar to those in the United States are seen in the developed countries in western Europe, Australia, and New Zealand. In the developing countries of Latin America, Africa, and Asia, cancer is a less important cause of death because of the continued impact of infectious and parasitic diseases and malnutrition on infant and childhood mortality (*6*).
2. *National Health Promotion and Disease Prevention Objectives, Healthy People, 1991* [DHHS Publication (PHS) 91-50212, Public Health Service, Washington, DC, 1991].
3. L. A. G. Ries, B. F. Hankey, B. K. Edwards, Eds., *Cancer Statistics Review 1973–1987* (NIH Publ. 90-2789, NIH, Bethesda, MD, 1990). The Surveillance, Epidemiology and End Results (SEER) Program was initiated in 1972 and is supported by the National Cancer Institute (NCI). There are currently ten participants (Connecticut; Detroit, Michigan; Iowa; Atlanta, Georgia; New Mexico; Utah; Seattle, Washington; San Francisco–Oakland, California; Hawaii; and Puerto Rico), and the total population covered represents slightly more than 10% of the U.S. total. The participants are required to report all new malignant and in situ neoplasms except nonmelanoma epithelial skin cancers. The latter cannot be reliably ascertained and have a minimal effect on cancer mortality.
4. D. Coggon *et al.*, *J. Natl. Cancer Inst.* **81**, 1178 (1989).
5. NCI, *Annual Cancer Statistics Review Including Cancer Trends: 1950–1985* (NIH Publ. 88-2789, NIH, Bethesda, MD, 1988).
6. L. Tomatis, Ed., *Cancer: Causes, Occurrence and Control* (World Health Organization, International Agency for Research on Cancer, Scientific Publ. 100, Lyon, France, 1990).
7. C. C. Brown and L. G. Kessler, *J. Natl. Cancer Inst.* **80**, 43 (1988).
8. J. A. H. Lee, *Photochem. Photobiol.* **50**, 493 (1989); M. L. Kripke, *Cancer Prev. (Philadelphia)* **89**, 1 (November 1989).
9. L. Bernstein, D. Levin, H. Menck, *Cancer Res.* **49**, 466 (1989); V. Beral, T. Peterman, R. Berkelman, *Lancet* **337**, 805 (1991); M. Gail *et al.*, *J. Natl. Cancer Inst.* **83**, 695 (1991).
10. E. White, C. Y. Lee, A. R. Kristal, *J. Natl. Cancer Inst.* **82**, 1546 (1990); B. A. Miller, E. J. Feuer, B. F. Hankey, *Cancer Causes Control* **2**, 75 (1991); E. R. Greenberg *et al.*, *N. Engl. J. Med.* **323**, 789 (1990).
11. P. Boyle, P. Maisonneuve, R. Saracci, *J. Natl. Cancer Inst.* **82**, 1594 (1990); N. H. Greig, L. G. Ries, R. Yancik, *ibid.*, p. 1621.
12. S. Preston-Martin, W. Mack, B. E. Henderson, *Cancer Res.* **49**, 6137 (1989).
13. M. C. Yu *et al.*, *J. Natl. Cancer Inst.* **77**, 351 (1986).
14. B. N. Ames and L. S. Gold, *Proc. Nat. Acad. Sci. U.S.A.* **87**, 7772 (1990).
15. B. E. Henderson, R. K. Ross, M. C. Pike, *Cancer Res.* **42**, 3232 (1982).
16. S. Preston-Martin *et al.*, *ibid.* **50**, 7415 (1990).
17. B. Vogelstein *et al.*, *Nature* **348**, 681 (1990); J. M. Nigra *et al.*, *ibid.* **342**, 705 (1989); P. A. Jones *et al.*, *Cancer Res.* **51**, 3617 (1991); M. Hollstein, D. Sidransky, B. Vogelstein, C. C. Harris, *Science* **253**, 49 (1991).
18. R. Doll and R. Peto, *J. Natl. Cancer Inst.* **66**, 1191 (1981).
19. W. J. Blot and J. F. Fraumeni, *Cancer Prev. (Philadelphia)* **89**, 1 (October 1989).
20. R. Peto, paper presented at the Fifteenth International Cancer Congress, Hamburg, Germany, 16–22 August 1990.
21. J. E. Buring and C. H. Hennekens, *Cancer Prev. (Philadelphia)* **89**, 1 (July 1989).
22. R. Doll, *Proc. Nutr. Soc.* **49**, 119 (1990); W. C. Willett *et al.*, *Lancet ii*, 130 (1983); W. C. Willett *et al.*, *N. Engl. J. Med.* **310**, 430 (1984); A. M. Y. Nomura *et al.*, *Cancer Res.* **45**, 2369 (1985); A. Nomura *et al.*, *J. Natl. Cancer Inst.* **79**, 103 (1987); M. S. Menkes *et al.*, *N. Engl. J. Med.* **315**, 1250 (1986); S. E. Schober *et al.*, *Am. J. Epidemiol.* **126**, 1033 (1987); K. J. Helzlsouer *et al.*, *Cancer Res.* **49**, 6144 (1989); N. J. Wald *et al.*, *Br. J. Cancer* **56**, 69 (1987); N. J. Wald, J. Boreham, J. L. Hayward, *ibid.* **49**, 321 (1984); J. T. Salonen *et al.*, *Br. Med. J.* **290**, 417 (1985); J. Virtamo *et al.*, *Cancer* **60**, 145 (1987); P. Knekt, *Int. J. Epidemiol.* **17**, 281 (1988); *Am. J. Epidemiol.* **127**, 28 (1988); P. Knekt *et al.*, *J. Natl. Cancer Inst.* **82**, 864 (1990); F. J. Kok *et al.*, *Am. J. Epidemiol.* **125**, 12 (1987); F. J. Kok *et al.*, *N. Engl. J. Med.* **316**, 1416 (1987); G. Fex *et al.*, *Nutr. Cancer* **10**, 221 (1987); H. B. Stähelin, R. Rösel, E. Buess, *J. Natl. Cancer Inst.* **73**, 1463 (1984); H. B. Stähelin *et al.*, *Am. J. Clin. Nutr.* **53**, 265S (1991).
23. W. S. Stryker *et al.*, *Am. J. Epidemiol.* **127**, 283 (1988); A. F. Subar, L. C. Harlan, M. E. Mattson, *Am. J. Public Health* **80**, 1323 (1990); D. W. Nierenberg *et al.*, *Am. J. Epidemiol.* **130**, 511 (1989).
24. Y.-T. Gao *et al.*, *Int. J. Cancer* **40**, 604 (1987); A. H. Wu-Williams *et al.*, *Br. J. Cancer* **62**, 982 (1990).
25. C. Muir *et al.*, Eds., *Cancer Incidence in Five Continents, 1987* (IARC Publ. 88, Lyon, France, 1987).
26. R. A. Cartwright *et al.*, *Lancet* **ii**, 842 (1982).
27. M. R. Law, *Br. J. Cancer* **59**, 686 (1989).

28. M. C. Yu, J. H. C. Ho, S. H. Lai, *Cancer Res.* **46**, 956 (1986).
29. J. V. Joossens and J. Geboers, *Nutr. Cancer* **2**, 250 (1981); P. Correa, *Cancer Res.* **48**, 3554 (1988); T. Hiryama, *Gann Monogr.* **11**, 3 (1971); W. Haenszel, M. Kurihara, M. Sequ, *J. Natl. Cancer Inst.* **49**, 969 (1972); L. Bernstein, B. Henderson, *J. Cancer Res. Clin. Oncol.* **110**, 184 (1985); S. Tsugane *et al.*, *Cancer Causes Control* **2**, 165 (1991).
30. W. C. Willett *et al.*, *N. Engl. J. Med.* **323**, 1664 (1990).
31. J. W. Morgan, G. E. Fraser, R. L. Phillips, *Am. J. Epidemiol.* **128**, 918 (1988).
32. W. Willett *et al.*, *N. Engl. J. Med.* **316**, 22 (1987).
33. P. K. Mills *et al.*, *Cancer* **64**, 582 (1989).
34. G. R. Howe, C. M. Friederreich, M. Jain, *J. Natl. Cancer Inst.* **83**, 336 (1991).
35. P. K. Mills *et al.*, *Cancer* **64**, 598 (1989).
36. A. W. Hsing *et al.*, *Cancer Res.* **50**, 6836 (1990).
37. G. N. Stemmerman, A. M. Y. Nomura, L. K. Heilbrun, *ibid.* **44**, 4633 (1984).
38. C. Garland *et al.*, *Lancet* **i**, 307 (1985).
39. T. Hiryama, in *Diet, Nutrition and Cancer*, Y. Hayashi *et al.*, Eds. (Japan Scientific Societies, Tokyo, 1986), p. 41.
40. P. Y. Jones *et al.*, *J. Natl. Cancer Inst.* **79**, 465 (1987).
41. R. K. Severson, A. M. Y. Nomura, J. S. Grove, *Cancer Res.* **49**, 1857 (1989).
42. M. J. Wargovich, V. W. Eng, H. L. Newmark, *Cancer Lett.* **23**, 253 (1984).
43. E. Lanza and P. Greenwald, *Cancer Prev.* ((*Philadelphia*) **89**, 1 (September 1989).
44. M. Shike and S. J. Winawer, *ibid.* **90**, 1 (February 1990).
45. R. L. Prentice and L. Sheppard, *Cancer Causes Control* **1**, 81 (1990).
46. G. Howe, *ibid.*, p. 99; J. E. Hiler and A. J. McMichael, *ibid.*, p. 101; W. C. Willett and M. D. Stampfer, *ibid.*, p. 103; R. L. Prentice and L. Sheppard, *ibid.*, p. 53.
47. W. J. Blot *et al.*, *Cancer Res.* **48**, 3282 (1988); J. M. Elwood, J. C. G. Pearson, D. H. Skippen, *Int. J. Cancer* **34**, 603 (1984).
48. S. Barra *et al.*, *Int. J. Cancer* **46**, 1017 (1990); A. J. Tuyns, G. Péqoiqnot, J. S. Abbatucci, *ibid.* **23**, 443 (1979).
49. A. H. Wu, A. Paganini-Hill, R. K. Ross, *Br. J. Cancer* **55**, 687 (1987); M. P. Longnecker *et al.*, *Cancer Causes Control* **1**, 59 (1990); U. A. Simanowski *et al.*, *Gut* **27**, 278 (1986).
50. M. P. Longnecker *et al.*, *J. Am. Med. Assoc.* **260**, 652 (1988).
51. G. Block, *Am. J. Clin. Nutr.* **53**, 2705 (1991).
52. E. R. Greenberg *et al.*, *N. Engl. J. Med.* **323**, 789 (1990).
53. B. E. Henderson, R. Ross, L. Bernstein, *Cancer Res.* **48**, 246 (1988).
54. T. J. A. Key and M. C. Pike, *Eur. J. Cancer Clin. Oncol.* **24**, 29 (1988).
55. ———, *Br. J. Cancer* **57**, 205 (1988).
56. L. Bernstein and B. Henderson, *Cancer Prev.* (*Philadelphia*) **90**, 1 (January 1990).
57. L. Bergkvist *et al.*, *N. Engl. J. Med.* **321**, 293 (1985).
58. L. Bernstein *et al.*, *Cancer Causes Control* **1**, 51 (1990); H. Shimizu *et al.*, *Br. J. Cancer* **62**, 451 (1990); T. J. A. Key *et al.*, *ibid.*, p. 631; M. C. Pike, in *Accomplishments in Cancer Research 1989*, J. G. Fortner and J. E. Rhodes, Eds. (Lippincott, Philadelphia, 1990), p. 327.
59. J. Casagrande *et al.*, *Lancet* **ii**, 170 (1979).
60. R. K. Ross, A. Paganini-Hill, B. E. Henderson, in *Genitourinary Cancer*, D. G. Skinner and G. Lieskovsky, Eds. (Saunders, Philadelphia, 1988), p. 40.
61. R. L. Noble, *Cancer Res.* **37**, 1929 (1977).
62. M. C. Bosland, *Prostatic Carcinogenesis* (University of Utrecht, Utrecht, 1989).
63. R. K. Ross *et al.*, *J. Natl. Cancer Inst.* **76**, 45 (1986).
64. B. E. Henderson *et al.*, *Br. J. Cancer* **57**, 216 (1988).
65. L. Bernstein *et al.*, *ibid.* **55**, 681 (1987); S. D. Harlow and G. M. Matanoski, *Am. J. Epidemiol.* **133**, 38 (1991).
66. D. Garabrant, J. Peters, T. Mack, *Am. J. Epidemiol.* **119**, 1005 (1984).
67. V. C. Jordan, *Cancer Prev.* (*Philadelphia*) **90**, 1 (August 1990); R. L. Prentice, *J. Natl. Cancer Inst.* **82**, 1310 (1990); D. V. Spicer, M. C. Pike, B. E. Henderson, *ibid.* **83**, 63 (1991).
68. L. Villard and M. Murphy, *Int. J. Epidemiol.* **19**, 255 (1990).
69. M. C. Pike *et al.*, *Br. J. Cancer* **60**, 42 (1989); D. V. Spicer *et al.*, *Contraception* **44**, 289 (1991).
70. B. E. Henderson *et al.*, *Br. J. Cancer* **48**, 437 (1983).
71. A. Herbst *et al.*, *Am. J. Obstet. Gynecol.* **154**, 814 (1986).
72. R. K. Ross *et al.*, *Cancer Res.* **49**, 1045 (1989); S. Patierno *et al.*, *ibid.*, p. 1038; A. Paganini-Hill, A. Chao, R. K. Ross, *Br. Med. J.* **299**, 1247 (1989).
73. S. Preston-Martin, D. C. Thomas, M. C. Yu, *Br. J. Cancer* **59**, 639 (1989).
74. D. C. Thomas and S. Preston-Martin, *Technical Report No. 32* (Department of Preventive Medicine, University of Southern California, Los Angeles, CA).
75. B. E. Henderson, *J. Natl. Cancer Inst.* **81**, 320 (1989).
76. R. P. Beasley, C. C. Lin, L. U. Hwang, *Lancet* **ii**, 1129 (1981); H. C. Whittle *et al.*, *ibid.* **337**, 747 (1991).
77. H. zur Hausen, *Science* **254**, 1167 (1991).
78. W. L. Peterson, *N. Engl. J. Med.* **334**, 1043 (1991).
79. D. Forman *et al.*, *Int. J. Cancer* **46**, 608 (1990); A. Nomura *et al.*, *N. Engl. J. Med.* **325**, 1132 (1991); J. Parsonnet *et al.*, *ibid.*, p. 1127.
80. J. Peto, B. E. Henderson, M. C. Pike, in *Banbury Report 9: Quantification of Occupational Cancer*, R. Peto and M. Scheiderman, Eds. (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1981), p. 51.

Tumor Suppressor Genes

ROBERT A. WEINBERG

For the past decade, cellular oncogenes have attracted the attention of biologists intent on understanding the molecular origins of cancer. As the present decade unfolds, oncogenes are yielding their place at center stage to a second group of actors, the tumor suppressor genes, which promise to teach us equally important lessons about the molecular mechanisms of cancer pathogenesis.

THE PROLIFERATION OF NORMAL CELLS IS THOUGHT TO BE regulated by growth-promoting proto-oncogenes counterbalanced by growth-constraining tumor suppressor genes. Mutations that potentiate the activities of proto-oncogenes create the oncogenes that force the growth of tumor cells. Conversely, genetic lesions that inactivate suppressor genes liberate the cell from the constraints imposed by these genes, yielding the unconstrained growth of the cancer cell. These two end results—deregulated growth resulting from oncogene activation or from suppressor gene inactivation—would seem to be similar if not identical. However, accumulating evidence suggests that they are indeed quite different physiologically and that the progression of many tumors to full malignancy requires both types of changes in the tumor cell genome.

The existence of tumor suppressor genes becomes most apparent when they are missing from cell genomes. This simple fact underlies the experimental difficulties in studying them and the attendant 10-year lag of this research behind that focused on oncogenes. But these barriers to progress have now been breached, due in large part to recently developed strategies of gene isolation. As a consequence, tumor suppressor genes promise as rich a harvest in the 1990's as oncogenes yielded a decade earlier (*1*). This review attempts to place these genes in a conceptual framework and to discuss in some detail six of these that have been isolated as molecular clones.

Whitehead Institute for Biomedical Research and Massachusetts Institute of Technology, Nine Cambridge Center, Cambridge, MA 02142.