Summary

Whether drug-based or target-based screens are used, it is possible to exploit the detailed information gathered for several model organisms that are genetically tractable. Such approaches are well suited to identifying drugs that have a selective killing capacity for the tumor context. They allow us to escape from strategies that are based on inhibiting the activities of oncogene products, or attempting to restore the lack of activity resulting from the inactivation of a tumor suppressor gene product. Because such genetic approaches allow an alignment of particular molecular defects with "specific" drugs, there is a high probability that the serious side effects associated with many currently used chemotherapeutics will be less problematic. Although the utility of genetics and model organisms is potentially quite broad, three inadequacies will continue to limit clinical applications. The first stems from the current difficulties in understanding the complexities of the mammalian cell signaling circuitry, the second stems from our still limited methods of assessing molecular alterations in tumors, and the third stems from relatively ineffective ways of conditional gene inactivation in mammalian cells. Finally, as more therapies are developed for particular molecular defects, there will be increased need as well as incentive to improve methods for detecting these alterations.

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Environment and Cancer: Who Are Susceptible?

Frederica P. Perera

Acting in concert with individual susceptibility, environmental factors such as smoking, diet, and pollutants play a role in most human cancer. However, new molecular evidence indicates that specific groups—characterized by predisposing genetic traits or ethnicity, the very young, and women—may have heightened risk from certain exposures. This is illustrated by molecular epidemiologic studies of environmental carcinogens such as polycyclic aromatic hydrocarbons and aromatic amines. Individual genetic screening for rare high-risk traits or for more common, low-penetrant susceptibility genes is problematic and not routinely recommended. However, knowledge of the full spectrum of both genetic and acquired susceptibility in the population will be instrumental in developing health and regulatory policies that increase protection of the more susceptible groups from risks of environmental carcinogens. This will necessitate revision of current risk assessment methodologies to explicitly account for individual variation in susceptibility to environmental carcinogens.

Most cancer results from the interaction of genetics and the environment (*1–3*). That is, genetic factors by themselves are thought to explain only about 5% of all cancer (*3*). The remainder can be attributed to external, "environmental" factors that act in conjunction with both genetic and acquired susceptibility. This is an optimistic message for cancer prevention in that exposure to environmental carcinogens—tobacco smoke, dietary constituents, pollutants (in the workplace, air, water, and food supply), drugs, radiation, and infectious agents—is theoretically preventable. But it challenges scientists to document environment-susceptibility interactions and policy-makers to rapidly

translate this knowledge into public health interventions. The pressure is great: 560,000 people die of cancer every year in the United States (6.6 million worldwide), and almost 1.4 million new cases are diagnosed in the United States annually (*4*).

The two parallel approaches in prevention are (i) strategies to help individuals modify hazardous lifestyles or use chemoprevention, and (ii) reduction of involuntary exposure to carcinogens, usually through regulation. Both approaches have been stymied by our inability to explicitly address risks to sensitive subsets of the population. Historically, policy-makers such as the U.S. Environmental Protection Agency have based their decisions on the assumption that all individuals in a population have the same biologic response to a specified dose of a carcinogen. These policymakers are only now becoming aware of the need to account for interindividual variation in susceptibility, especially as it affects risks to children (*5*, *6*).

What do we know about risks to specific populations? With respect to specific exposures? Specific cancers? How can this knowledge be applied to cancer prevention?

Here, I discuss in some detail four categories of susceptibility factors—genetic predisposition, ethnicity, age, and gender—and, more briefly, health and nutritional impairment (Fig. 1). Molecular epidemiology, a relatively new approach that uses biomarkers to study risk factors in populations, has documented striking interactions between exposure and susceptibility factors in determining cancer risk. I will draw upon molecular data from three representative types of biomarkers: polymorphisms in genes encoding metabolic/detoxification enzymes, carcinogen-DNA adducts, and mutational spectra in reporter genes. Much of the research relates to variation in susceptibility to two classic environmental carcinogens: polycyclic aromatic hydrocarbons (PAH), generated from the combustion of fossil fuels, and aromatic amines, which are present in cigarette smoke and other environmental media. Both PAH and aromatic amines are major etiologic factors in lung, bladder, and possibly breast cancers. These examples vividly illustrate the complexity of environment-susceptibility interactions.

The selected biomarkers are mechanistically relevant to cancer (*1*, *7*, *8*). Variations in the expression or form of the so-called metabolic genes, such as the P450, glutathione S-transferase (GST), and *N*-acetyltransferase (NAT) genes, strongly influence individual biologic response to carcinogens. Carcinogenic residues bound to DNA or surrogate proteins (known as adducts) provide both a fingerprint of exposure and an indicator of procarcinogenic DNA damage. In general, more PAH-DNA adducts are formed in persons who smoke or are exposed to PAH in the workplace and ambient air. However, various studies have shown considerable interindividual variation in carcinogen-DNA binding (on the order of a 30- to 50-fold difference) under equivalent conditions of exposure (*1*). PAH-DNA adducts, especially those formed by the carcinogen benzo[a]pyrene (BP) diol epoxide (BPDE), have been linked to an increased risk of lung cancer (*9*). Similarly, smokers have more hemoglobin adducts formed by the aromatic amine 4-aminobiphenyl (4-ABP); a number of studies have associated these adducts with an increased risk of bladder cancer (*10*). Finally, the *P53* tumor suppressor gene is mutated in 40 to 50% of lung, breast, colon, and other common tumors; the mutational spectrum varies by cancer type and by environmental exposure, providing clues to the specific risk factors involved (*8*). In some cases, the patterns have been consistent with both the types of DNA adducts and the mutations induced experimentally by the compound (*8*, *11*). For example, *P53* mutations in lung and breast tumors are predominantly G → T transversions, which are induced experimentally by BP and are increased in a dose-dependent manner in smokers with lung cancer (*8*, *12*). Coming full circle, it appears that the formation of both adducts and *P53* mutations in response to exposure is strongly modulated by polymorphisms in metabolic genes. Thus, these three types of biomarkers have been proposed to be early indicators of cancer risk, although there is debate over their specific application to public health policy (*1*, *7*, *13*).

Genetic Susceptibility

Genetic factors that contribute to cancer susceptibility include rare, highly penetrant, dominant mutations as well as more common genetic polymorphisms that influence individual response to environmental exposures (*1–3*, *13*, *14*). Retinoblastoma, Wilms' tumor, and a subset of breast and ovarian cancers (Li-Fraumeni syndrome) are examples of cancers affected by rare, dominant mutations. Other "high-risk" genetic disorders are xeroderma pigmentosum (XP) and ataxia telangiectasia (AT). These traits can confer very high lifetime cancer risks to the affected individuals, but they explain only a small fraction of cancer incidence.

Although they pose low individual risk, more common genetic traits—such as those that influence the metabolic activation or detoxification of carcinogenic chemicals—

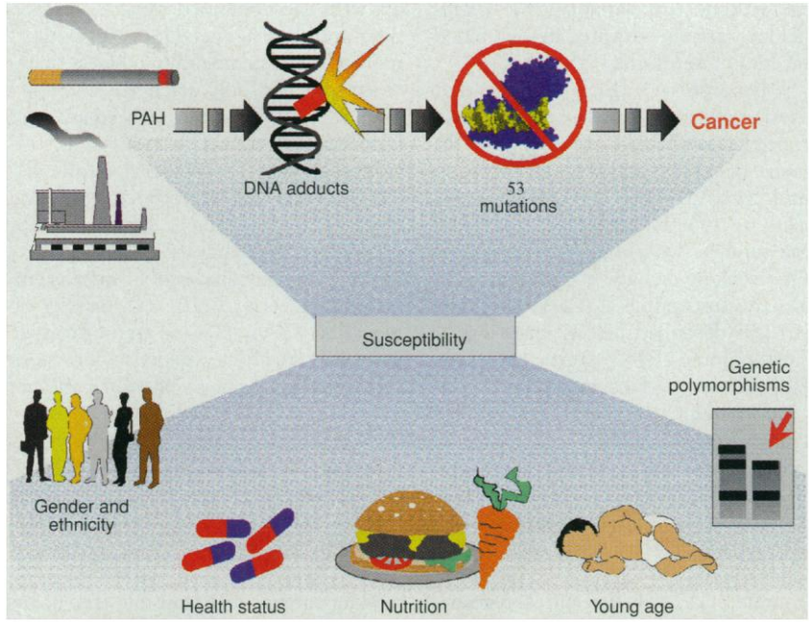

Fig. 1. A proposed pathway for environmental carcinogenesis, which begins when exposure to PAH, formed from incomplete combustion processes, leads to the formation of PAH-DNA adducts. These adducts can cause mutations in critical genes such as *P53*. The mutations alter the normal functions of the proteins; in this case, the DNA-binding domain of *P53* (blue) loses the ability to complex with DNA (yellow). A succession of mutations in other critical genes leads to cancer. The entire pathway is thought to be influenced by susceptibility factors such as gender and ethnicity, health status, nutrition, young age, and genetic polymorphisms. Molecular epidemiologic approaches are currently being used to investigate this proposed pathway and the role of these suspected susceptibility factors.

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can be important determinants of population risk. For example, the phase I cytochrome P450 enzymes catalyze the oxidative metabolism of diverse endogenous and exogenous chemicals from steroids to pollutants; during the oxidative process, electrophilic and carcinogenic intermediates can be created. Many P450 genes are polymorphic, including *CYP1A1*, whose product metabolizes PAH such as BP. About 10% of the Caucasian population has a highly inducible form of the enzyme that is associated with an increased risk of lung cancer in smokers. Although not all studies have been positive, in Japanese and certain Caucasian populations, increased lung cancer risk is correlated with one or both *CYP1A1* polymorphisms, the so-called Msp I polymorphism and the closely linked exon 7 (isoleucine-valine) polymorphism (*15–17*). The greatest incremental lung cancer risk from the "susceptible" *CYP1A1* genotype was seen in light smokers (seven times the risk of light smokers without the genotype), whereas heavy smokers with this genotype had less than twice the risk of heavy smokers without the genotype (*15, 16*). The proposed mechanisms for this phenomenon are higher *CYP1A1* inducibility or enhanced catalytic activity of the valine-type CYP1A1 enzyme. Consistent with these mechanisms, U.S. smoking volunteers with the exon 7 mutation were found to have more PAH-DNA adducts in their white blood cells than were smokers without the variant (*18*). PAH-DNA adducts are also elevated in cord blood and placenta of newborns with the *CYP1A1* MSP1 polymorphism, which suggests that the genetic polymorphism may increase risk from transplacental PAH exposure (*19*). In lung tissue of adults, adduct concentration correlates with *CYP1A1* expression or enzyme activity (*7*). Finally, lung tumors of Japanese smokers were found to be significantly more likely to have *P53* mutations if they had the susceptible *CYP1A1* genotype (*15, 16*). As described below, variation in other cytochrome P450 genes (such as *CYP1A2*, whose product metabolizes aromatic and heterocyclic amines) can also modulate cancer risk (*10*).

In contrast to the phase I activating enzymes, phase II enzymes—epoxide hydrolase, GST, NAT, and sulfotransferase—generally detoxify carcinogenic metabolites to produce excretable hydrophilic products. For example, *GSTM1* detoxifies reactive intermediates of the carcinogens PAH, ethylene oxide, and styrene. In about 50% of Caucasians, the *GSTM1* locus is entirely deleted; a number of studies have associated *GSTM1* deletion with an increased risk of bladder and lung cancer (*20, 21*). The importance of gene-environment interactions is illustrated by the finding that individuals with the null genotype had little risk of bladder cancer in the absence of exposure to tobacco smoke. In lung biopsies, the frequencies of PAH-DNA adducts and *P53* mutations were higher in persons with the *GSTM1* null genotype (*22–24*). Finally, susceptibility to aflatoxin B_1 (AFB_1)–induced hepatocellular carcinoma has been associated with the deletion of *GSTM1* in combination with the epoxide hydrolase genotype that is correlated with low activity of the detoxification enzyme (*25*).

NAT2 deactivates carcinogenic aromatic amines through N-acetylation; 50 to 60% of Caucasians and 30 to 40% of African-Americans are "slow" acetylators (*26*). Some, but not all, studies indicate that persons with the *NAT2* slow acetylator genotype have a higher risk of bladder cancer if they are exposed to environmental carcinogens such as 2-naphthylamine and 4-ABP (*10*). With low exposure to tobacco smoke, slow acetylators had approximately twice as many 4-ABP–hemoglobin adducts as did rapid acetylators; however, with higher exposure, NAT2 had no effect on adduct concentration. Among postmenopausal women, smoking increased breast cancer risk only among those with the *NAT2* slow acetylator genotype (*27*).

Not only can multiple genes modulate the effects of environmental carcinogens, but interactions between genes can result in a greater-than-additive effect on risk. Smokers with the combined rapid CYP1A2 oxidizer and slow N-acetylation phenotype had more 4-ABP–hemoglobin adducts than other smokers, but only when the smoking dose was low (*10*). Research with Japanese populations has revealed that individuals with the combination of the *CYP1A1* (Val/Val) and *GSTM1* null genotypes, relative to persons with neither genotype, have an eightfold increase in frequency of *P53* mutations (*15, 16*) and an estimated sixfold increase in risk of lung cancer (*15, 16, 28*). Studies of the role of CYP1A1 and GST in lung cancer risk in Caucasians have yielded inconsistent results, possibly because of ethnic differences in gene prevalence or linkage.

Much of this research suggests that common genetic polymorphisms in P450s and *NAT2* have a greater impact on procarcinogenic adducts and cancer risk when exposure to carcinogens is low. Although this pattern was not seen with *GSTM1* and bladder cancer, it is plausible that at higher exposures, the effects of certain genetic traits are overwhelmed by the environmental insults.

DNA repair capacity also varies between individuals as a result of inheritance, environmental challenges, and physiologic factors. The activities of two specific DNA repair enzymes—O^6-alkyldeoxyguanine-DNA alkyltransferase and uracil DNA glycosylase—differ by as much as 180-fold and 300-fold, respectively, in the human population (*29*). Decreased efficiency or fidelity in repair, in the absence of high-risk syndromes such as AT and XP, has been clearly linked to increased cancer risk. Relative to healthy controls, patients with lung cancer were five times as likely to have reduced ability to repair damage induced by BPDE (*30*).

In addition, genetic variation in receptors that are instrumental in the toxicokinetics of carcinogens can strongly influence cancer risk. Individuals with the high-affinity dioxin-binding aromatic hydrocarbon (Ah) receptor are likely to have greater risk from dioxin and PAH, because by binding to the receptor, these chemicals up-regulate *CYP1A1*, *CYP1A2*, and other genes, thereby stimulating their own metabolism (*31*). Affinity differences in the estrogen, androgen, and peroxisome proliferator-activated receptors may also be important determinants of susceptibility (*31*).

With respect to individual screening for the genetic traits just discussed, there is a growing awareness of associated technological problems, the potential for misuse of genetic information, and the limited effectiveness of this information in the prevention of cancer. According to the National Advisory Council for Human Genome Research, it is premature to offer testing of either high-risk families or the general population as part of general medical practice (*13*). However, as will be discussed, knowledge of the prevalence and distribution of common genetic susceptibility factors can be of considerable benefit in risk assessment and cancer prevention.

Susceptibility Related to Ethnicity or Race

Epidemiologic data show that ethnic and racial groups differ significantly in terms of cancer incidence and mortality rates (*4, 32*). For example, relative to white Americans, black Americans have cancer incidence rates that are approximately three times as high for esophageal cancer; twice as high for multiple myeloma, liver, cervical, and stomach cancer; and 50% higher for cancers of the oral cavity and pharynx, larynx, lung, prostate, and pancreas. The incidence of chronic lymphocytic leukemia, multiple myeloma, and premenopausal breast cancer is also higher in black Americans. In contrast, white Americans have higher incidence rates for melanoma, leukemia, lymphoma, and cancers of the endometrium, thyroid, bladder (in males), ovary, testis, and brain, as well as postmenopausal breast cancer (*4, 32*). Hispanics have gen-

erally lower cancer rates than white or black Americans, but rates differ substantially among Hispanics by race (*1*).

Molecular data also demonstrate ethnic differences. The spectrum of *P53* mutations in breast cancer varies between black and white women and between Japanese and Western women. In a California population, serum concentrations of the organochlorine 1,1′-dichloro-2,2′-bis(*p*-chlorophenyl) ethylene (DDE), a metabolite of 2,2′-bis(*p*-chlorophenyl)-1,1,1-trichloroethane (DDT), were found to be higher among black women than among white women (*33*). In black smokers, urinary concentrations of metabolites of the tobacco-specific carcinogen 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and serum concentrations of cotinine (a metabolite of nicotine) exceeded those in white smokers (*34*). Although unmeasured differences in exposure cannot be ruled out, these findings are consistent with biologic variation and with the higher rates of various smoking-related cancers in blacks.

Although the precise function of the *BRCA1* gene is not known, female carriers of *BRCA1* gene mutations have an 80 to 90% lifetime risk of breast cancer. In contrast to the varied *BRCA1* mutations seen in the non-Jewish population, a specific mutation (185delAG) has been found in about 1% of the Ashkenazi Jewish population (*35*). Relative to noncarriers, carriers of this mutation have an estimated 27-fold increase in the risk of early-onset breast cancer (*35*).

Among the biologic factors that might explain higher cancer risks in certain ethnic or racial groups are variations in the prevalence of genetic traits affecting carcinogen metabolism and DNA repair. The stronger association between DDE serum concentrations and breast cancer in black women relative to white women may reflect genetic differences affecting the induction by chlorinated hydrocarbons of enzyme-mediated estrogen metabolism (*36*). The *GSTM1* null genotype occurs less frequently among blacks (35%) than whites (49%) (*21*). The NAT2 slow acetylator phenotype occurs in about 50% of whites, compared with 35% of blacks and 14% of Asians (*26*), consistent with ethnic or racial differences in bladder cancer rates. A trend corresponding to that for NAT2 was seen in 3- and 4-ABP–hemoglobin adducts across the three groups, with the highest concentration of adducts observed in persons with both the *GSTM1* null and slow acetylator profile (*26*). Polymorphisms in other genes have been implicated in racial variation in cancer incidence; these include the h-*ras*, 5-alpha-reductase, and NAD(P)H quinone oxidoreductase genes (*37*). It is clear, however, that no one ethnic or racial group is exempt from genetic susceptibility to carcinogens, nor is any group at uniformly higher risk than another.

Racial or ethnic variation in cancer risk may reflect differences in environmental exposure or socioeconomic and demographic factors as well as innate biologic susceptibility. The rise in breast cancer rates experienced by the descendants of Asian immigrants to the United States provides strong evidence that environmental factors affect cancer patterns. After several generations, the rates in Asian Americans are the same as those prevailing in the U.S. white population (*32, 38*). Within the United States, substantial ethnic or racial variations in the extent of environmental exposure to certain pollutants have also been noted (*1*).

Age-Related Susceptibility

There are important age-related differences in susceptibility to environmental toxicants (*1, 5, 6*). Experimental and epidemiologic data indicate that, because of differential exposure or physiological immaturity, infants and children have greater risk than adults from a number of environmental toxicants, including PAH, nitrosamines, pesticides, tobacco smoke, air pollution, and radiation. The underlying mechanisms may include increased absorption and retention of toxicants, reduced detoxification and repair, the higher rate of cell proliferation during the early stages of development, and the fact that cancers initiated in the womb and in the early years have the opportunity to develop over many decades.

Relative to body weight, infants and children take in appreciably more food, water, and air—and any carcinogens contained in them—than do adults. The very young may also have uniquely high exposures from nursing and other behaviors. For example, relative to adults with background exposure, nursing infants have an estimated 10- to 20-fold greater average daily intake of dioxin, a carcinogen that accumulates in breast milk (*39*). Molecular epidemiologic studies also indicate that the young have a higher internal dose of toxicants or greater genetic damage than adults who are similarly exposed to tobacco smoke and PAH. In cord blood of newborns at delivery, concentrations of cotinine were significantly higher (by 70%) than in the mothers' blood, also sampled at delivery (*19*). Infants also had 30% more PAH-DNA adducts than their mothers (although this difference was not statistically significant, this finding is noteworthy because the internal dose of PAH to the fetus is estimated to be about one-tenth of that to the mother). Similarly, in young children, urinary concentrations of 1-hydroxypyrene glucuronide, an indicator of PAH exposure, were higher than those in their mothers (*40*).

Adolescence and young adulthood are also viewed as sensitive life stages because of greater proliferative activity in epithelial cells of certain tissues. Women who were in their teens at the time of the atomic bombings had the greatest risk of radiation-induced breast cancer (*1*). Similarly, initiation of smoking at an early age confers a higher risk of lung, bladder, and possibly breast cancer. The risk of lung cancer for women who began smoking before age 25 is almost four times that for women who began after age 25 (*41*). Breast cancer risk associated with the *NAT2* slow acetylator genotype is higher in women who began smoking under the age of 16 (*27*). Similarly, long-term use of oral contraceptives by young women and exposure to human papilloma virus at an early age have been associated with enhanced risk of breast and cervical cancer, respectively (*1*).

Susceptibility in the elderly has received less attention in research. However, immune function and DNA repair efficiency both decrease with age, which reduces protection against environmental carcinogens (*1*).

Gender-Related Susceptibility

Hormonal factors play an obvious role in breast cancer and may also explain the higher rates of thyroid and gall bladder cancer in women (*32*). In general, absolute cancer rates are higher in males than in females. However, several lines of evidence suggest that, dose for dose, women are inherently more susceptible to certain carcinogens than men. A number of epidemiologic studies indicate that women smokers are 1.7 to 3 times as likely as male smokers to develop lung cancer, given the same amount of exposure (*12, 42*). Smoking and estrogen replacement therapy may interact to increase the risk of lung cancer in postmenopausal women (*12*). Possible mechanisms that may underlie the enhanced susceptibility of women are slower plasma clearance of nicotine (which is a precursor to NNK), greater activity of CYP P450 enzymes, enhanced formation of DNA adducts and *P53* mutations, and hormonal effects on tumor promotion (*42*). For example, the concentration of PAH-DNA adducts and the frequency of *P53* mutations (specifically G:C → T:A transversions) were elevated by 40% and 60%, respectively, in lung tumors from female smokers relative to those from male smokers (*12, 23, 43*). Moreover, the *P53* transversions were associated with the *GSTM1* null genotype. Consistent with these findings, a recent case-control study of lung cancer found the

effect of the *GSTM1* null genotype on lung cancer risk to be significant only among women (*44*).

Preexisting Health and Nutritional Impairment

Immunological impairment, preexisting disease, and nutritional deficits can also increase susceptibility to carcinogens. For example, epidemiologic studies have shown that fruits and vegetables rich in antioxidants and other micronutrients have a protective effect against diverse cancers, including lung, esophageal, oral, laryngeal, cervical, and breast. These micronutrients may act through a variety of mechanisms to block DNA damage, mutation, and carcinogenesis by oxygen radicals, PAH, and other chemical carcinogens. Recent studies indicate that heavy smokers with low plasma concentrations of certain micronutrients, such as alpha-tocopherol and specific carotenoids, may have reduced protection against carcinogen-induced DNA damage (*18*, *45*). However, in several studies, these effects were seen only in smokers who also had the *GSTM1* null genotype (*45*), illustrating the fact that multiple susceptibility factors are involved in individual responses to environmental challenges. Sensitivity to mutagens, measured by bleomycin-induced chromatid breaks in cultured lymphocytes, was also increased in healthy individuals with low plasma concentrations of antioxidants (*46*).

Application to Cancer Prevention

I have highlighted a number of different genetic and acquired susceptibility factors that modulate individual responses to environmental carcinogens. Most of these factors are not rare events in the population (Table 1). This is obvious for young age, ethnicity, and gender, but is also true for genetic susceptibility. The increasing evidence of the importance of relatively common metabolic polymorphisms supports the comment by Francis Collins that "there are no perfect specimens" in terms of resistance to disease (*47*).

Molecular data illustrate the complexity of environment-susceptibility interactions—not one gene but multiple genes are involved, and the effects of these genes can be modified by ethnicity, age, gender, nutritional status, and extent of carcinogen exposure. Despite its complexity, this body of knowledge holds much potential in terms of cancer prevention. First, it has immediate application to the identification of environmental risk factors. In epidemiology, it has been difficult to detect relative risks of 1.5 or even 2.0. [The relative risk is the ratio of disease rates in exposed versus unexposed groups (where "exposure" is the characteristic under study). A relative risk of 2 indicates a doubling of risk among the exposed group.] Causal relations and underlying mechanisms may emerge more clearly when etiologic research is focused on subgroups with heightened sensitivity (*36*). Second, the greatest strides in preventing cancer at the population level will come from interventions that protect the susceptible subgroups. Thus, knowledge of differential risk resulting from predisposing metabolic genetic traits, ethnicity, young age, gender, or health and nutritional impairment can be useful in developing regulations, public education, health surveillance, behavior modification programs, and chemoprevention strategies that will have the maximum impact.

In recent years, there have been numerous, often controversial, proposals to consider information on the mechanism or mode of action in assessing the risks of individual carcinogens (*48*). However, there is increasing recognition that it is equally important—perhaps more important—to incorporate available knowledge about the distribution of exposure and susceptibility within the population into the risk assessment process, replacing the fallacious default assumption of population homogeneity (*6*, *49*). Wherever possible, for each toxicant of concern, risk assessments should present the estimated range of risk across the population as well as risks to identified sensitive populations, which might include children, genetically susceptible subgroups, women, or specific ethnic groups. Preventive policies could then be targeted, and regulations written, to protect

Table 1. Known or potential biologic susceptibility factors in cancer (*1*). FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colon cancer; VTR, variable tandem repeat; EtO, ethylene oxide.

Type	Factor	Type of cancer	Putative mechanism
Genetic factors			
Rare inherited syndromes	Li-Fraumeni	Breast, other	Loss or inactivation of tumor suppressor gene
	Rb	Retinoblastoma	
	Wilms tumor	Bladder	
	BRCA1	Breast	
	FAP	Colon	
	HNPCC	Colon	Defective DNA repair
	XP	Skin	
	AT	Breast, other	
Common inherited genetic variants*	CYP1A1	Lung, other	Altered metabolism (substrate: PAH)
	CYP2D6	Lung	Altered metabolism (substrate: NNK)
	GST	Lung, bladder	Decreased detoxification (substrates: PAH, EtO, styrene, AFB_1)
	NAT2	Bladder, breast	Decreased detoxification (substrate: 4-ABP)
	O^6-Alkyldeoxyguanosine	Lung, other	Inefficient DNA repair
	h-ras-1 VTR	Lung, breast, other	Unknown
Ethnicity	Genetic and environmental	Various	Differing prevalence of genotypes and environmental patterns of exposure
Age	Physiologic	Breast, lung, other	Decreased detoxification, DNA repair, and immune function with early or old age
Gender	Hormonal	Breast, other	Deregulation of growth and differentiation through receptor binding
	Metabolic	Lung, other	Differing metabolic/detoxification patterns
Preexisting impairment	Immunologic, chronic disease, nutritional	Liver, lung, breast, cervical, other	Decreased immune function, altered metabolism, detoxification, reduced repair, deregulation of growth and differentiation

*Associations reported in some, but not all, studies. Risks are strongly dependent on exposure.

those sensitive groups that are likely to bear disproportionate risk, thus reducing the incidence of cancer and avoiding environmental inequities (*50*).

In modeling risk distribution and identifying susceptible populations, molecular epidemiology can be a useful tool, provided that the biomarkers are adequately validated and study designs are sound (*1*, *49*). Biomarkers can also contribute to risk assessment by providing dose-response data for extrapolation from laboratory animals to humans, by elucidating mechanisms in human carcinogenesis, and by serving as intermediate endpoints for monitoring the effectiveness of interventions.

Cancer is largely a preventable disease. Molecular epidemiology has contributed to the growing awareness of the importance of relatively common genetic and acquired susceptibility factors in modulating risks from environmental carcinogens. To make greater strides in preventing cancer, we need public health strategies that reflect this knowledge.

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Recent Advances in Chemoprevention of Cancer

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Chemoprevention is the use of pharmacologic or natural agents that inhibit the development of invasive cancer either by blocking the DNA damage that initiates carcinogenesis or by arresting or reversing the progression of premalignant cells in which such damage has already occurred. Recent advances in our understanding of the mechanisms of carcinogenesis have led to the synthesis of new drugs that can inhibit tumor development in experimental animals by selective action on specific molecular targets, such as the estrogen, androgen, and retinoid receptors or inducible cyclooxygenase. Several of these agents (including tamoxifen, 13-*cis*-retinoic acid, retinyl palmitate, and an acyclic retinoid) are clinically effective in preventing the development of cancer, particularly in patients who are at high risk for developing second primary tumors after surgical removal of the initial tumor.

In spite of immense efforts to improve treatment and find cures for advanced disease, overall mortality rates for most forms of epithelial cancer have not declined in the past 25 years. The prognosis for a patient with metastatic carcinoma of the lung, colon, breast, or prostate (four of the most common and lethal forms of cancer, which together account for more than half of all deaths from cancer in the United States) remains dismal (*1*). A current scientific view indicates that damage to numerous regulatory genes ultimately results in the development of invasive and metastatic cancer, which is the culmination of the chronic disease process, carcinogenesis. The natural history of carcinogenesis and cancer provides a strong rationale for a preventive