Cancer Prevention in Clinical Medicine

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Populations at Low Risk

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In studying cancer etiology, it is as important to identify populations at relatively low risk (8,34) as it is to identify populations at relatively high risk (13). From those at low risk, clues to protective mechanisms emerge; from those at high risk, clues to causative mechanisms emerge.

The objective of studying populations that develop chronic diseases at relatively low rates compared with the general population is to understand the protective factors that minimize or delay an individual's risk of developing and dying from cancer, heart disease, and other serious illness. A number of epidemiologic studies have examined relatively low rates of disease around the world (1,4,23,26, 34,52,61a,63). These have been directed at both coronary heart disease (26) and cancer (4,23,34). Based on these findings, apparent risk factors can hopefully be minimized.

This chapter presents an extensive epidemiologic review of the cancer mortality and incidence experience of the major low-risk populations in the United States. It should be noted that these data are derived from observations of naturally occurring populations and not from controlled experimental studies on humans, since such experiments are extremely difficult and expensive to conduct (39a, 47a).

DEFINITIONS

Cancer Incidence, Cancer Mortality, and Total Mortality

The cancer incidence rate is the annual probability of a person developing cancer, and the cancer mortality rate is the annual probability of a person dying from cancer (4). The total mortality rate is the annual probability of dying from any cause, and this probability integrated over all ages determines life expectancy (4,5,17). Ideally, an assessment of risk should include both cancer incidence and mortality. However, cancer incidence has not been determined for nearly as many subgroups of the U.S. population as has cancer mortality. Cancer incidence can often be estimated from data on cancer mortality, and both measures have strengths and weaknesses, as discussed elsewhere (4). This chapter focuses on subpopulations of the U.S. because these have the most relevance to other Americans. In most U.S. adult populations,

TABLE 1. *Age-adjusted death and cancer incidence rates for several average risk reference populations*

Reference population	Age-adjusted death rates (deaths/10⁵): Total mortality, Males	Total mortality, Females	Total cancer, Males	Total cancer, Females	Age-adjusted incidence rates (cases/10⁵): Total cancer, Males	Total cancer, Females	References
Standardized to 1970 U.S. population							
A 1970 U.S. whites	1,180.7	698.6	198.9	132.6			(60,64)
B 1960 U.S. whites	1,225.3	786.6	182.2	135.6			(17,60)
C 1950 U.S. whites	1,275.9	894.6	169.1	147.5			(17,60)
D 1959–61 U.S. whites	~1,206	~779	~182	~135			(17,28)
E 1950–69 U.S. whites	~1,224	~799	~186	~142			(35,36)
F 1973–77 U.S. whites	~1,086	~630	207.1	133.1			(64)
G 1973–77 SEER whites			209.5	136.9	371.6	301.2	(64)
H 1969–71 TNCS whites					342.5	270.4	(2)
Standardized to 1960 U.S. population							
B 1960 U.S. whites	1,144.9	720.8	171.1	128.6			
D 1959–61 U.S. whites	1,126.9	713.5	~171	~128			
E 1950–69 U.S. whites			174.0	130.1			
Special populations							
S.1 1968–72 U.S. whites, aged 35–74 years							(48)
S.2 1966–68 U.S. whites, aged 35–84 years							(10)
S.3 1955 U.S. white males							(27)
S.4 1950–61 U.S. white males							(54)
S.5 1960–72 ACS total cohort							(14,15)
S.6 1954–69 U.S. veteran total cohort							(46,47)

cancer comprises 15 to 20% of all deaths and total cardiovascular disease comprises 75 to 80% of all noncancer deaths. Some data are included on cancer and total death rates in a few selected foreign populations for reference purposes.

Average Risk

The "average risk" is defined here to be that of the U.S. white population, circa 1970, who comprised 87% of all Americans in 1970. The most detailed and accurate cancer incidence and mortality data are avialable on U.S. whites, and most published epidemiologic comparisons have involved U.S. whites, making this group the most logical and convenient choice for an average risk population. The age-adjusted death rates for all causes and for all cancers are shown in Table 1 for various U.S. white populations since 1950, identified by letters A through H. For those few instances where published data do not allow comparison with U.S. whites of all ages, special reference populations have been used and are identified as S.1 through S.6. All measures of risk used here are based on age-adjusted rates, because aging is a prime determinant of cancer incidence and mortality rates, as will be discussed later.

Full Low-Risk Populations

Low risk is defined as a cancer mortality or incidence rate significantly below the average rate experienced by the U.S. white population. Full low risk, in addition to meaning low risk for cancer, also includes low risk for total mortality. Most healthy populations, such as various groups of nonsmokers, fall into this category. In full low-risk populations, cancer still accounts for 15 to 20% of all deaths, and the risk factors for cancer deaths often apply to total mortality as well. Full low risk means that longevity is increased in the population in addition to its having a reduced cancer risk. These populations are of greatest interest as models for disease prevention and extensive data on them are presented in Tables 2, 3, and 4.

Partial Low-Risk Populations

Partial low risk means low risk for total cancer but not for total mortality. The cancer rate may or may not be accurately measured. In some parts of the world, such as Africa, India, and Latin America, cancer is very poorly diagnosed, and, hence, cancer rates appear to be very low for the simple reason that the disease is underreported. However, the total mortality rate, which is usually a more accurately compiled indicator in these same countries, is substantially higher than that in the U.S., chiefly due to high death rates from infectious diseases, malnutrition, and other causes (63). Consequently, some of the residents of these countries avoid cancer simply by dying young from other causes. These foreign and native populations are not practical examples for disease prevention in the U.S. Also, some populations in several geographic areas of the U.S. have low cancer rates, but average or high total death rates (48).

TABLE 2. *Basic description of the low-risk populations*

Years	Population description	Size: Males	Size: Females	Methodology	References
Representative nonsmokers				Mortality-census sample survey	(10)
1966–68	U.S. representative white nonsmokers of cigarettes (35–84 yr):				
	(never smokers)	9,525,416	23,945,722		
	(former smokers)	7,607,781	2,705,964		
High socioeconomic status populations				Mortality-census sample survey	(28)
1960	U.S. representative whites with 13+ years of education (25+ yr)	8,415,007	7,175,169		
Insured populations				Prospective cohort study	
	U.S. Metropolitan Life Insurance Company individual standard ordinary policyholders (20+ yr)				
1955–60	First and 16th+ policy years				(55)
1968–69	All policy years				(56,57)
Married populations				Mortality-census sample survey	
1959–61	U.S. white married persons (15+ yr)	41,831,000	42,575,000		(28)
1966–68	U.S. representative white married persons (35–84 yr)	29,351,000	26,708,800		(10)
Healthy questionnaire respondents				Prospective cohort study	
1954–69	U.S. veteran questionnaire respondents (30+ yr):				(25,44–47)
	Never or occasional only smokers	55,049			
	Ex-smokers who stopped for other than physician's orders	43,758			
1960–72	25 states American Cancer Society Cancer Prevention Study questionnaire respondents who never smoked regularly (30+ yr)	94,436	375,381		(14,15,21,22)
Healthy religious groups				Mortality-census survey	
Mormons					
1967–75	Utah Mormons (all ages)	380,821	400,914		(32)
1970	Utah Mormons (35+ yr)				(9)
1968–75	California Mormons (35+ yr)	56,361	68,708		(9)
1968–75	California active Mormons (35+ yr)	13,879			(9)
1970–75	Utah active Mormons (35+ yr)	50,391			(9)
Seventh-Day Adventists				Prospective cohort study	
1960–76	California Seventh-Day Adventists (35+ yr)	8,116	14,824		(41)
Clergy					
1950	U.S. white clergymen (20–64 yr)	96,227			(18)
1950–60	U.S. white protestant clergymen (20+ yr)	28,134			(27)
Special occupational groups					
1950	U.S. all employed whites (20–64 yrs)	36,301,644		Mortality-census survey	(18,19)
1950	U.S. professional, technical, & kindred workers (20–64 yr)	2,862,527			(18,19)
1950	U.S. white physicians (20–64 yr)	152,891			(18,19)
1941–51	U.S. physicians (20+ yr)	204,450			(3)
1969–73	U.S. physicians (20+ yr)	317,789			(16)
1950–79	California physicians (25+ yr)	10,130		Prospective cohort study	(10a)
1950–61	U.S. sample from 1950–51 *Who's Who in America* (45+ yr)	5,800		Prospective cohort study	(54)
Ethnic groups				Mortality-census survey	
Japanese Americans					
1960	U.S. Japanese (5+ yr)	88,105	84,708		(28)
1959–62	U.S. Japanese (35+ yr)	155,697	151,239		(20)
1950–69	U.S. Japanese (all ages)	92,995	109,786		(36)
1968–72	Japanese in California, Hawaii, & New York (35+ yr)				(31)
Spanish Americans					
1973–77	New Mexico Hispanics (all ages)	215,507	221,214		(64)
American Indians					
1960	U.S. Indians (5+ yr)	158,639	164,337		(28)
1950–69	U.S. Indians (all ages)				(37)
1969–71	U.S. Indians (all ages)	41,308	44,492		(58)
1973–77	New Mexico Indians (all ages)				(64)
Geographically defined populations				Mortality census survey	
Special states and counties					
1950–69	Utah whites (all ages)	436,198	437,630		(35)
1950–69	New Mexico whites (all ages)	442,352	433,411		(35)
1950–69	Baldwin Co. Georgia whites (all ages)	9,724	10,844		(35)
1950–69	Washington Co. Utah whites (all ages)	5,116	5,023		(35)
1970	Utah whites (all ages)	508,997	522,929		(6)
1970	New Mexico whites (all ages)	452,120	463,695		
1973–77	New Mexico whites (all ages)	522,929	463,695		(64)
Special State economic areas				Mortality census survey	
1968–72	Colorado East Central SEA 9 counties (35–74 yr)	23,474	23,852		(48)
1968–72	Utah south SEA 17 counties (35–74 yr)	64,247	64,458		(48)
1968–72	Utah north SEA 7 counties (35–74 yr)	54,350	54,529		(48)
Special countries				Mortality-census survey	
1970	Sweden (all ages)	~4,000,000	~4,000,000		(1,63)
1970	Japan (all ages)	~55,000,000	~55,000,000		(1,52,63)
1969–73	Japan (all ages)				(31)
1962–64	Mexico City (15–74 yr)	887,176	1,059,607		(42)
1970	Mexico (all ages)	24,065,614	24,159,624		(1,63)

TABLE 3. *Standardized ratios for total mortality and total cancer comparing each low risk study population with the appropriate average risk reference population*[a]

Years	Study population	Reference population	Outcome measure	Total mortality Males	Total mortality Females	Total cancer Males	Total cancer Females
Representative nonsmokers							
1966–68	U.S. white never smokers	S.2	MR	74	84	63	85
		S.2	SMR			67	87
	Never and former smokers	S.2	SMR	83	92	79	94
High socioeconomic status populations							
1960	U.S. whites 13+ yr education	B	MR	89	72	92	93
Insured populations							
1955–60	Metropolitan Life Insurance Standard Ordinary policyholders						
	First policy year	D	MR	~30	~30		
	16th+ policy years	D	MR	~77	~83		
	All policy years	A	MR	~80	~90	91	107
Married populations							
1959–61	U.S. white married persons	D	MR	89	92		
1966–68	U.S. white married persons	S.2	SMR	~87	~85	93	92
Healthy questionnaire respondents							
1954–69	U.S. veterans: never smokers	B	MR	~50		~50	
	ex-smokers	B	MR	~61		~70	
	never smokers	S.6	SMR	~70		~71	
1960–72	U.S. ACS never smokers	A	MR	~55	~75	50	82
		S.5	SMR			64	96
Healthy religious groups							
Mormons							
1967–75	Utah Mormons	H	SIR			73	76
1970	Utah Mormons	A	MR	79	82		
1968–75	California Mormons	A	MR	67	79		
1968–75	California Mormons		SMR			68	83
1968–75	California active Mormons	A	MR	48		50	
1970 & '75	Utah active Mormons	A	MR	52		49	
Seventh-Day Adventists							
1960–76	California Adventists	A	SMR	53	63	51	68
Clergy							
1950	U.S. white clergymen	C	SMR	92		88	
1950–60	U.S. white protestant clergy	S.3	SMR	72		63	
Special occupational groups							
1950	U.S. all employed whites	C	SMR	102		100	
1950	U.S. white professional, technical, & kindred workers	C	SMR	87		91	
1950	U.S. white physicians	C	SMR	101		83	
1949–51	U.S. physicians	C	SMR	93		93	
1969–73	U.S. physicians	A	MR	73			
1950–59	California physicians	S.3	SMR	84		86	
1970–79	California physicians	F	SMR	67		64	
1950–61	*Who's Who in America* sample						
	All prominent men	S.4	MR	70			
	Prominent clergymen	S.4	MR	61			
Ethnic groups							
Japanese Americans							
1960	U.S. Japanese	B	MR	66	68		
1959–62	U.S. Japanese	D	SMR	68	71	104	73
1950–69	U.S. Japanese	E	MR			91	64
1968–72	Japanese in California, Hawaii and New York	A	SMR			84	73
Spanish Americans							
1973–77	New Mexico Hispanics	G	IR			76	79
American Indians							
1960	U.S. Indians	B	MR	124	137		
1950–69	U.S. Indians	E	MR			57	84
1969–71	U.S. Indians	A	MR	143	87		
1973–77	New Mexico Indians	F	MR			47	78
1973–77	New Mexico Indians	G	IR			48	64
Geographically defined populations							
Special states and counties whites							
1950–69	Utah State	E	MR			76	78
1950–69	New Mexico	E	MR			78	88
1950–69	Baldwin Co., Georgia	E	MR			41	29
1950–69	Washington Co., Utah	E	MR			57	70
1970	Utah	A	MR	90	91	75	77
1970	New Mexico	A	MR	100	102	77	91
1973–77	New Mexico	F	MR			87	103
1973–77	New Mexico	G	IR			89	97
Special state economic areas whites							
1968–72	Colorado E. Central 9 counties	S.1	MR	81	73	59	70
1968–72	Utah South 17 counties	S.1	MR	85	83	66	63
1968–72	Utah North 7 counties	S.1	MR	76	79	62	65
Special countries							
1970–71	Sweden	A	MR	77	92	87	102
1970	Japan	A	MR	~90	~100	92	86
1969–73	Japan	A	SMR			93	87
1962–64	Mexico City	B	MR	111	155	56	103
1970	Mexico	A	MR	124	169	37	69

[a] IR = incidence ratio; SIR = standardized incidence ratio; MR = mortality ratio; SMR = standardized mortality ratio.

TABLE 4. *Standardized ratios for five major cancer sites comparing each low-risk study population with the appropriate average-risk reference population*

Years	Study population	Reference population	Outcome measure	Lung cancer Males	Lung cancer Females	Colorectal cancer Males	Colorectal cancer Females	Pancreas cancer Males	Pancreas cancer Females	Prostate Males	Breast Females
Representative nonsmokers											
1966–68	U.S. white never smokers	S.2	SMR	22	53	128	90	60	83	83	94
	Never and former smokers	S.2	SMR	55	70	109	93	74	85	88	103
High socioeconomic status populations											
1960	U.S. white 13 + yr education	B	MR	70	97	95	75			117	118
Insured populations											
1968–69	All policy years	A	MR	110	81			92	108	89	109
Married populations											
1959–61	U.S. married whites	D	MR	~93	~93	~96	~93	~96	~94	~99	~96
Healthy questionnaire respondents											
1954–69	U.S. veterans										
	Never or occasional-smokers	S.6	SMR	21		93		81		93	
	Ex-smokers	S.6	SMR	83		116		95		110	
1960–72	ACS never smokers	S.5	SMR	17	64	87	101	64	92	95	100
Healthy religious groups											
Mormons											
1967–75	Utah Mormons	H	SIR	33	28	55	55	70	41	108	78
1968–75	California Mormons	A	SMR	58	78	70	78	63	83	77	93
1968–75	Calif active Mormons	A	SMR	23		64		46		79	
1970–75	Utah active Mormons	A	SMR	19		54		71		105	
Seventh-Day Adventists											
1960–76	California Adventists	A	SMR	11	23	56	51			86	89
Clergy											
1950	U.S. white clergymen	C	MR			154					
1950–60	U.S. white protestant clergymen	S.3	SMR	35		74		79		94	
Special occupational groups											
1950	U.S. employed whites	C	SMR	101		101					
1950	U.S. white professional, technical, and kindred workers	C	SMR	82		119				87	
1950	U.S. white physicians	C	SMR	59		103				102	
1950–59	California physicians	S.3	SMR	62		96		136		127	
1970–79	California physicians	F	SMR	30		67		82		80	
Ethnic groups											
Japanese Americans											
1950–69	U.S. Japanese	E	MR	98	100	71	52	110	97	34	24
1968–72	Japanese in California, Hawaii and New York	A	SMR	60	68	85	80	88	89	47	31
Spanish Americans											
1973–77	New Mexico	G	IR	35	81	40	61	138	165	86	57
American Indians											
1950–69	U.S Indians	E	MR	34	72	81	45	69	103	58	41
1973–77	New Mexico Indians	F	MR	11	08	25	26	35	174	77	40
1973–77	New Mexico Indians	G	IR	14	18	23	40	66	181	71	25
Geographically defined populations											
Special states and counties whites											
1950–69	Utah	E	MR	58	52	72	65	82	78	110	81
1950–69	New Mexico	E	MR	65	100	52	67	91	102	89	76
1950–69	Baldwin Co. Georgia	E	MR	47	25	23	18	61	46	45	24
1950–69	Washington Co. Utah	E	MR	21	41	57	48	29	82	83	84
1973–77	New Mexico	F	MR	74	108	76	92	105	118	100	82
1973–77	New Mexico	G	IR	80	102	67	85	120	129	106	92
Special state economic areas											
1968–72	Colorado East Central	S.1	MR	53	38	75	64	76	38		75
1968–72	Utah south	S.1	MR	48	36	33	66	92	56		75
1968–72	Utah north	S.1	MR	36	19	63	44	38	97		68
Special countries											
1970	Sweden	A	MR	44	92	92	88			132	85
1970	Japan	A	MR	34	54	50	49			14	20
1969–73	Japan	A	SMR	36	59	53	51	67	66	16	20
1962–64	Mexico City	B	MR	28	48	31	27	57	93	27	61
1970	Mexico	A	MR	17	43	14	19			41	23

Site-Specific Low-Risk Populations

Site-specific low risk means low risk of developing cancer in some parts of the body but high risk of the disease at other sites, resulting in approximately average total risk of developing cancer. This definition applies to most populations reported to have around average total risk, because some sites will be at low risk while others will be high risk. For instance, among native Japanese, breast and colon cancers are relatively rare, but the frequency of stomach cancer is great. Consequently, the total cancer rate among Japanese is only about 10% less than among U.S. whites (31,52).

Erroneous Low-Risk Populations

Erroneous low risk applies to those populations in whom the cancer rate is considered low but is not accurately determined, and the total mortality rate may or may not be genuinely low. Members of relatively primitive societies, such as the small principality of Hunza in West Pakistan, the village of Vilcabamba in Ecuador, and the highlands of Georgia in the Soviet Caucasus, are often reported in the popular press to live to extremely old ages, frequently in excess of 100 years, and experience little or no cancer (29,61). Only upon closer inspection do we find that these areas do not maintain any formal birth, death, or longevity records and do not have doctors qualified to diagnose cancer properly (37a). Hence, most of these extraordinary claims have no scientific validity. Until scientifically rigorous studies of these groups can be completed, such reports must be treated with skepticism. Even if these populations are eventually shown to have genuinely low cancer rates, their austere and primitive life-styles are not likely to be of practical interest to Americans.

Theoretical Low-Risk Populations

Theoretical low risk is an epidemiologic exercise that sums the minimum rate for individual cancer around the world to arrive at a theoretical minimum risk for all cancer. This has been done most extensively by Higginson (23) and Doll (4) and shows that the theoretical minimum rate is about 20% of the average rate and less than 10% of the theoretical maximum rate. We present data based on minimum rates in U.S. counties and list economic areas relative to the national average. These calculations usually ignore the competing risk factors that tend to increase one form of cancer while decreasing another form in a given person, and are used only to estimate the theoretical preventability of cancer. These data are contained in Tables 5 and 6.

Preventability of Cancer

The general concept that most cancers occur as a result of life-style and other environmental factors and are generally preventable was recognized by an expert

committee of the World Health Organization (WHO) in 1964 (62). The committee stated that:

> The potential scope of cancer prevention is limited by the proportion of human cancers in which extrinsic factors are responsible. These [factors] include all environmental carcinogens (whether identified or not) as well as "modifying factors" that favour neoplasia of apparently intrinsic origin (e.g., hormonal imbalances, dietary deficiencies and metabolic defects). The categories of cancer that are thus influenced, directly or indirectly, by extrinsic factors include many tumours of the skin and mouth, the respiratory, gastrointestinal and urinary tracts, hormone dependent organs (such as the breast, thyroid and uterus), haematopoietic and lymphopoietic systems, which, collectively, account for more than three-quarters of human cancers. It would seem, therefore, that the majority of human cancer is potentially preventible.

The committee included, in addition to man-made or natural carcinogens, viral infections, nutritional deficiencies or excesses, reproductive activities, and a variety of other factors determined wholly or partly by personal behavior. The avoidance of cancer is to be accomplished only by means that might conceivably be socially acceptable. Potentially acceptable measures might, for example, include a continuation of the current decrease in cigarette smoking or tar yields, which would reduce the risk of lung cancer, but would not include a first pregnancy for most females by 15 years of age, even though this would reduce the risk of breast cancer.

In the years since that report was published, these opinions have been consolidated and many researchers now accept its main conclusion. As mentioned above, some researchers have gone further and have arrived at figures of 80% or even 90% as the proportion of potentially preventable cancers in place of the 1964 committee's cautious estimate of "the majority." However, these conclusions remain to be demonstrated in actual human populations.

An ambiguity in what is meant by the "preventability" of cancer arises simply because everyone is bound to die sooner or later. If exactly half the cancer deaths that now occur were somehow magically prevented and nothing else changed, those people who would have died of cancer might live for an additional 5, 10, 20, or 30 years (the average being 10 or 15 extra years), but they must eventually die of something and that something would, for some of them, be a second cancer. Even so, we would still describe such a change as a halving of the cancer rate. Conversely, if every cause of death other than cancer were suddenly abolished, then of course everyone would eventually die of cancer, although it might be misleading to describe such a change in terms of an increase in either the risk of cancer or the average age at death from cancer, especially if one were interested in the causes of cancer. The usual means of avoiding these ambiguities is to avoid basing inferences on the percentages of people who "will eventually" die of cancer, on "crude" cancer rates, or on "the mean age at death from cancer." Instead, it is usual to restrict attention to "age-specific" and "age-adjusted" cancer rates, discussed next. The avoidance of a certain percentage of cancer implies a reduction by that percentage in the age-adjusted rates.

MAJOR SYSTEMIC FACTORS INFLUENCING LEVEL OF RISK

Aging and Age Adjustment

In spite of the fact that a number of investigators do not care to deal with this variable, there is no doubt that aging is by far the most important risk factor in cancer mortality. The annual risk of death from cancer increases about 200-fold with advancing age from about 0.1% at age 25 to about 2% at age 85 (17,36). Consequently, all rates discussed here have been made comparable with respect to age by using direct age adjustment to the standard 1940, 1950, 1960, or 1970 U.S. populations or other similar U.S. populations (17,60). The age-adjusted death rate is a weighted average of the age-specific death rates, using as the weights the age distribution of one of the standard U.S. populations. Age-adjusted death and incidence rates for several average risk reference populations are presented in Table 1. Disease outcome measures in this chapter are presented in terms of ratios of age-adjusted incidence rates (IR) or mortality rates (MR), or in terms of indirectly age-adjusted ratios, known as standardized incidence ratios (SIR), or standardized mortality ratios (SMR). A ratio of 100 indicates the population under study has the same rate as the standard population. Detailed explanations and examples can be found in several references (4,17,64).

Reliability of Population and Mortality Data

This is obviously a major determinant because the risk measurement is only as good as the data upon which it is based. As mentioned earlier, in countries with poor vital statistics systems cancer cases and deaths of all kinds often go unreported, and populations at risk are inaccurately determined. This is why the cancer rates in many underdeveloped countries are reported to be ridiculously low, in a number of international comparisons based on available data (1,63). The only way to avoid this problem is to restrict our analysis to those populations where the vital statistics and population-at-risk measures are reliable and accurate.

Effects of Selection on Mortality

The results obtained in a mortality investigation must be interpreted as reflecting not only the characteristics of the individuals under study but also the manner in which they have been selected for inclusion in the study. For instance, death rates among persons insured under individual life insurance policies reflect the fact that the lives accepted for insurance have been screened with the aid of medical examinations or related inquiries, and that such persons had both the financial means and the need for the insurance (5,55). Persons who have been recently accepted for individual life insurance after a medical examination can be regarded as ostensibly free from at least the more serious physical impairments. For some years after issuance of the insurance their mortality continues to be distinctly lower than that of the general body of insured persons at the same age. With the passage of time, however, this differential in mortality diminishes.

In recent years, early death rates of men insured under individual life policies have been very low compared to those of men in the general population—during the first year of insurance only 25 to 35% of those for white men in the general population (55). After 15 years have elapsed since issuance of the insurance, the effects of the initial screening usually disappear, but the death rates of insured lives still remain substantially below corresponding population mortality rates because the persons insured under individual life policies have for the most part been drawn from the middle and better-to-do segments of the population and generally engage in relatively healthy life-styles (5,55).

Questionnaire Respondent Effect

Another form of selection involves people who complete health questionnaires as part of epidemiologic cohort studies (14,21,25,47). These persons tend to be healthier than average, with SMR values often as low as 70 to 80%, often because of their superior initial health status. The implications of this effect are not adequately appreciated. For instance, the mortality rates among the persons included in the American Cancer Society Cancer Prevention Study appeared at first glance to be unusually low in the first 6 months or first year of observation, as compared with the contemporaneous death rates in the general population, but were found to be closely in line with the corresponding death rates of insured lives within 6 months or a year after issuance of the insurance (21,55). The U.S. veterans study analyzed this effect in detail by following all veterans who were sent a questionnaire, including those who did not respond. The questionnaire respondents relative to all veterans were found to have a total death rate that was 8% lower in the first three years of follow-up and 5% lower after eight years of follow-up (25). This topic will be discussed further in connection with individual studies.

However, this phenomenon does not apply to truly random cohorts selected from the general population. Monson showed that the 1925 to 1975 follow-up of 4,431 members of a general population in the Boston area produced SMRs close to 100% relative to U.S. whites (39). Over this fifty year period 50% of the men and 44% of the women died and 33% of the men and 34% of the women were lost to follow-up, but this was accounted for in a program for calculating expected deaths by assuming that the mortality experiences of persons lost to follow-up do not differ from those of persons who continue under follow-up. The SMR for all causes is 91% for men and 99% for women; SMR for all cancer is 105% for men and 102% for women. This demonstrates that a random sample of people followed for mortality over a long period tend to have average death rates.

Healthy Worker Effect

Occupational groups are often described as consisting of "healthy workers" because their mortality rates are lower than those of the national average (11,12,38,53). The "healthy worker effect" is actually more complicated than this and involves a combination of initial selection factors, healthy life-styles, and inadequate mortality follow-up. For instance, in a study of all industrial workers ever exposed to vinyl chloride in Great Britain, three factors have been shown to contribute to the low mortality rates that were observed: the selection of a healthy population for employment, the survival in the industry of the healthier men, and the length of time that this population has been pursued (12). The mortality experience within 5 years of entering this industry was shown to be as low as 37% of that expected; for circulatory disease and respiratory disease it was as low as 21%. There was a progressive increase in the SMR with the length of time since entry, so that the effect had almost disappeared 15 years after entry. To avoid confounding the selection effect with the survival effect, the latter was measured by separating men who survived 15 years after entering the industry according to whether they were still in the industry after this period. Those who left experienced an overall SMR some 50% higher than those still in the industry.

The decline of the healthy worker effect with the passage of time after the identification of a cohort of already active U.S. asbestos and rubber products workers has also been shown (38). When follow-up of a total cohort is achieved, including those that quit or retire early for health reasons, the initial healthy worker effect associated with active employment declines with time because of the absence of any continued selection process. For total mortality, the effect in this cohort disappeared after 5 years largely due to the increase in cancer mortality in the second and third quinquennial period of follow-up. Another study of workers in five U.S. chemical plants attempted to locate all white male employees who worked at least 12 months over a 25- to 30-year period (53). The results indicate that the mortality experience of the chemical workers studied is essentially that of the general U.S. population. This study suggested that the "healthy worker effect" may be due in part to methods frequently employed in searching for death claims, which understate the true experience of the employee group studied, or if present, may not affect mortality rates for neoplastic or cardiovascular disease. The unusually low death rates reported among some occupational cohorts could also be due to good health habits, such as reduced cigarette smoking (11). It is difficult to interpret occupational data when life-style characteristics are not given. Since over 90% of middle-aged American men are employed they must have death rates similar to the rates for all middle-aged American men, and this in fact was shown to be the case in the national occupational survey discussed later (18,19).

DESCRIPTION OF LOW-RISK POPULATIONS

The number of populations examined with respect to cancer risk is so vast that it is not possible to undertake an exhaustive review in this chapter. We have limited this examination to U.S. populations, plus the countries of Sweden, Japan, and Mexico, for reasons to be explained later. Furthermore, we have restricted coverage to the largest epidemiologic studies in terms of population or cohort size and person-years of observation. Also, we have only included populations examined by several investigators with results presented in high-quality scientific publications. We have tried to make use of the major publications for each type of population, but many other publications are not cited. Poorly defined or relatively small populations, where results are questionable or inconsistent, have been omitted. Also, only a few specially selected occupational groups have been covered. Specific inclusions and exclusions will be discussed briefly for each type of population.

A basic description of each examined population is given in Table 2, which shows time, location, size, age range, methodology, and special characteristics. Table 3 presents standardized ratios (SIR, SMR, IR, or MR) for total mortality and total cancer for each low-risk study population relative to the appropriate average-risk reference population. From this table it is possible to identify those populations at full low risk or partial low risk, which are the only categories we have attempted to cover here. Actual age-adjusted death rates can be obtained by multiplying the standardized ratio in Table 3 by the appropriate reference population rate in Table 1. Table 4 gives standardized ratios for the five major cancer sites (lung, colorectal, pancreas, breast, and prostate) for these same low-risk populations.

Representative Nonsmokers

This was a cross-sectional, two-sample study conducted by the National Center for Health Statistics (NCHS) to estimate the relative mortality risk of nationally representative nonsmokers in the total U.S. population (10). One sample was representative of U.S. deaths during 1966–1968, and the other resembled the general U.S. population during the same period. The smoking characteristics of both samples were determined, and mortality rates were then calculated as a function of smoking status. Estimates of observed deaths of nonsmokers 35 to 84 years of age in the U.S. in 1966–1968 were based on the National Mortality Survey, a follow-back survey linked to a probability sample of 19,526 death registration records that included deaths of 11,318 white men and 5,636 white women. Questionnaires were mailed to surviving family members and others named on the death certificates, who provided smoking histories and social characteristics of the deceased. The other source of data was the Current Population Survey conducted by the U.S. Bureau of the Census in August 1967. Smoking and socioeconomic information comparable to that for the decedent was obtained by means of household interviews for a probability sample of 60,920 noninstitutionalized adults 35 to 84 years of age, including 25,266 white men and 29,308 white women. The mortality ratios observed in this study are in good agreement with those in other major smoking studies (14,47).

High Socioeconomic Status Populations

The 1960 Matched Records Study was designed to provide nationwide statistics on mortality differentials in the U.S. by various social and economic characteristics collected in the April 1, 1960 census (28,59). The sample of deaths selected for the study was limited to persons who died during the four months from May through August 1960 and included all decedents under 65 years old, half of the decedents

65 to 74 years old, and one-fifth of the decendents 75 years and older. The net result was that 340,033 of the 534,623 U.S. deaths were included in the study and searched in the complete stage I 1960 census records.

The social and economic differentials in mortality derived from the study are based on ratios of actual to expected deaths, in which actual deaths were obtained as the sum of "matched deaths classified by social and economic characteristics as reported on their census schedules plus unmatched deaths classified by social and economic characteristics as estimated from NCHS survey questionnaires for the sample of unmatched deaths included in the survey," and expected deaths were obtained by multiplying 1960 age-specific death rates for the total population of the U.S. by the 1960 age composition of the subpopulation in each category of the social and economic characteristics for which mortality ratios were calculated (28).

Insured Populations

Insurance companies are the oldest and largest collectors of epidemiologic data because of their studies of policyholders; however, the data are infrequently used for epidemiologic purposes (5,56,57). At the time of selection, policyholders are at low risk, since they usually do not have serious illness or disease. This phenomenon is similar to the selection effect discussed earlier and is presented in data from the Society of Actuaries and the Metropolitan Life Insurance Company (55,56). The mortality of persons covered under group life insurance—who are predominantly males—resembles that of males insured under individual policies after more than 15 years have elapsed since issuance of the individual insurance, but is somewhat higher than that of males insured under individual policies to begin with (55). This is because the standards for group life insurance are much less selective than those for individual life insurance, the principle requirement being simply that the person to be covered by group life insurance be actively at work.

Married Populations

It has been known for decades that married persons have lower death rates than the population as a whole. Data on them has been collected as part of the national survey on differential mortality by socioeconomic and marital status described above (28). Other data on mortality by marital status is routinely collected as part of national death certificate and census data (17,30) or representative sample surveys (10). However, the effect is relatively small because married persons constitute the majority of the total population.

Healthy Questionnaire Respondents

Insured U.S. Veterans

Cancer mortality among nonsmokers, defined as persons who never or only occasionally smoke cigarettes, cigars, or pipes, was studied in an insured group of U.S. Veterans (25,44–47). A questionnaire concerning the use of tobacco, usual occupation, industry, and residence was mailed to about 300,000 active U.S. Government Life Insurance policyholders who were primarily veterans of World War I. Usable replies were received from about 200,000 persons (68%) from the first mailing and 49,000 from the second, yielding an 85% response. Deaths were established by a copy of the official death certificate sent to the investigator whenever a claim was filed. For the first group of respondents, additional medical information, including verification of the causes of death and procedures used to establish diagnoses, was requested from the physician who signed the death certificate or from the hospital where the death occurred. Almost all policyholders were white men from middle and upper socioeconomic classes. The Veterans Administration provided the names of policyholders who died during the study period and made special searches for about 75,000 persons whose insurance policies had terminated at the end of the study. The overall follow-up was considered to be almost 100% complete with respect to the fact and year of death. Mortality ratios are presented that compare never smoking veterans with veterans as a whole and with U.S. white males, since these veterans as a whole comprise an unusually healthy cohort.

American Cancer Society Cancer Prevention Study Cohort

The American Cancer Society (ACS) prospectively followed a cohort of 456,480 men and 590,562 women selected from 1,121 counties in 25 states for a "Cancer Prevention Study" on cancer mortality from 1960–1972 (14,15,21,22). Information on family history, history of disease, present physical complaints, occupational exposures, education, and eating, drinking, and smoking habits was collected via questionnaire. Sixty-eight thousand American Cancer Society volunteers enrolled an average of 16 persons each, initially 30 to 84 years old, between October 1959 and February 1960. Each year the volunteers were asked to report on the vital status and current address of the persons they enrolled. Every other year for 6 years the subjects completed a brief questionnaire giving details on hospitalizations, smoking habits, and other questions. The final follow-up resulted in the successful tracing of 93% of the subjects through September 1972. Most of the subjects were white, generally not ill, and generally above average in socioeconomic status at the time of enrollment. Mortality ratios are presented that compare never smoking respondents with all ACS respondents and with U.S. whites, since the ACS cohort as a whole is unusually healthy.

Healthy Religious Groups

Mormons

Mormons are an interesting religious group because their "Word of Wisdom," a Church doctrine since 1833, advises against the use of tobacco, alcohol, coffee, tea, and addictive drugs and recommends a well-balanced diet, particularly the use of whole grains, fresh fruits and vegetables, and moderation in the eating of meat

(6,7,9). Furthermore, the Church emphasizes a strong family life, conservative social mores, and good health practices in general. The Mormon Church, officially known as The Church of Jesus Christ of Latter-Day Saints, has approximately 3 million members in the U.S. and about 5 million members worldwide, including about 400,000 in California and 1,000,000 in Utah.

The mortality rates were based on Mormon Church membership and death records stored at Church headquarters in Salt Lake City, Utah and assembled from annual ward reports by church clerks throughout the world (6,7,9). Membership and death information from these reports were obtained for essentially all the California wards during 1968 through 1975, and all the Utah wards during 1970 and 1975. Identifying information for each deceased Mormon was matched with corresponding information on California and Utah death tapes. These deaths were then tabulated by age, sex, priesthood level, and cause. Death rates and standardized mortality ratios were calculated.

Cancer incidence during 1967–1975 was compared between Utah Mormons and non-Mormons utilizing data from the Utah Cancer Registry (32,33). For each of the cancer cases identified by the Registry, ascertainment of church membership was made possible with the use of the Church's central membership file. The Utah Mormon population was obtained from the annual church membership reports and the age distribution was estimated from a 5% systematic sample of the church population taken in August 1971.

Seventh-Day Adventists

Seventh-Day Adventists (SDAs) are a conservative religious denomination founded in 1863. Currently there are about 3 million members worldwide, 600,000 in North America, and 120,000 in California (40,41). By church proscription, virtually all SDAs abstain from use of tobacco and alcohol, and a large majority adhere to other church recommendations regarding other health habits. Presently, about half of all SDAs follow a lacto-ovo vegetarian diet, and few regularly use caffeine-containing beverages. They also tend rather sparingly to use sweets, other highly refined foods, hot condiments, and spices. Regularity in vigorous exercise and adequate rest, as well as conservative social mores, are strongly encouraged among SDAs.

The SDA subjects for this study consist of white respondents to the same four-page self-administered questionnaire used in the ACS Cancer Prevention Study in 1960. Every two years a very brief follow-up questionnaire was also collected, and this served as the primary method of death ascertainment in the SDA population during 1960–1965. The 1966–1976 deaths in the SDA group were ascertained solely by a computer-assisted record linkage with the California death tapes with some deaths being missed (41).

Clergy

Another religious study examined 28,134 U.S. clergymen from five Protestant denominations (American Baptist Church, United Lutheran Church in America, Protestant Episcopal Church, United Presbyterian Church, and Lutheran Church—Missouri Synod) during 1950–1960 (27). These are primarily white married clergymen in the above-average social class of professionals, and they constituted 16% of the total U.S. white clergy under 65 years of age in 1950. Approximately 90% of the study group were active clergymen (mostly parish ministers) and 10% were retired. The analysis was based on 5,207 deaths that occurred during 1951–1960 abstracted from death certificates or other sources. Demographic information on clergymen in each denomination for this study period was provided by the respective church pension office, but there are no data available on their life-style and health habits. The person-years of exposure contributed by the clergy over the ten years were determined after the number of withdrawals by termination of services or by death was taken into consideration. Also, data on all clergy are presented as obtained from the national occupational survey discussed next (18).

Special Occupational Groups

The National Occupational Survey is the first and only national study to determine mortality rates by cause for all major occupational groups in the United States (18,19,59). These surveys have been done regularly in England, with the most recent one covering 1970–1972 deaths (43). The primary sources of information for the U.S. study were microfilm copies of 1950 death certificates and 1950 population census schedules, or other equivalent documents. The occupation codes and procedures used were those developed for the 1950 Census of Population. The occupation information on both the vital record and the census schedule was reported by the wife for many of the men. The vital records call for "usual occupation" and the industry in which this occupation was followed. More than 90% of the vital records for men 20 to 64 years old contain an occupation report. In the 1950 census, information was requested for each person in the current labor force, on occupation, industry, and class of worker, relating to present job or last job.

This study is based on 230 sample areas, comprising 453 counties and independent cities in the U.S. Within each selected area, the specific cases were chosen by random sampling methods, and the sampling ratios were adjusted accordingly. The deaths sample was drawn from the complete mortality file. Data from this survey are presented for white clergymen, white male physicians, and white men of all occupations combined. Note that 36.3 million white men aged 20 to 64 years in 1950 had work experience, and that their death rate was essentially identical to that of all 39 million white men aged 20 to 64 years. This cross-sectional analysis reveals no healthy worker effect and indicates that workers, as a whole, have essentially the same death rates as the general population.

Physicians have been selected as one well-defined low-risk group of professional workers, who have been studied for several decades. Physician mortality experience was observed during 1949–1951 and 1969–1973 and compared to that of U.S. whites (3,16). Deaths were obtained from American Medical Association files based on death certificates from state and city departments of health and health services.

The population at risk was based on the age distribution of the physician population enumerated by the American Medical Association. Age-specific and age-adjusted death rates for U.S. physicians were compared with the corresponding data for the U.S. whites. Physician mortality rates were also determined in 1950 as part of the national occupational survey described above (18).

Mortality trends over thirty years have been described among a cohort of California male physicians (10a). The cohort was established using the 1950 American Medical Directory and followed for mortality through 1979 using the same sources described above. Standardized mortality ratios for the physicians were calculated relative to contemporaneous U.S. white males. This study is particularly interesting because it shows a large relative decline in lung cancer among the physicians that is most likely due to their greatly reduced cigarette smoking over this time period.

Prominent men have been examined as another low-risk group of professionals who are highly selected on the basis of achievement. Mortality during 1950–1961 was observed among a one-sixth sample of prominent men listed in the 1950–1961 edition of *Who's Who in America* and it was compared with that for all men in similar vocations in the general population of the U.S. (54). Men aged 45 years and over were distributed by vocation in the following manner: educators and business executives each accounted for about 21% of the total, lawyers and judges each 9%, men of letters 8%, clergymen, scientists, physicians, and surgeons each almost 6%, and military personnel and government officials each about 5%.

Ethnic Groups

Japanese in the U.S. and Japan

Cancer mortality risk was observed among all Japanese in the U.S. for the time periods of 1960 (28), 1959–1962 (20), 1950–1969 (36), and 1969–1971 (58) and among Japanese in Hawaii, California, and New York City during 1968–1972 (31). The main data sources come from state vital statistics offices, the National Center for Health Statistics, and the U.S. Bureau of the Census. For comparison with the homeland, data on cancer mortality in Japan were obtained for 1969–1973 (31,52).

Spanish Americans

Cancer incidence rates have been determined recently among Hispanics. However, there are inherent difficulties in obtaining a consistent definition of the Hispanic ethnic group on cancer incidence reports, death certificates, and census records. Consequently, the cancer rates for Hispanics are not as well established as those among Japanese. Extensive data have been obtained for New Mexico Hispanics, as part of the Surveillance, Epidemiology, and End Results (SEER) program (64).

The SEER program is conducted in ten geographic areas under contract with a local medical organization that is required to maintain a cancer information reporting system in the geographic area of coverage (64). This program has collected 1973–1977 cancer incidence, mortality, and survival data and has been ongoing since the 1969–1971 Third National Cancer Survey (2). Use is made of records on cancer patients seen in every hospital in and outside the area where resident patients are diagnosed or treated for active cancer. Additionally, all death certificates on which cancer is mentioned, records of private laboratories and nursing homes, and other relevant sources are used to determine valid incidence rates. Annual mortality tapes from the National Center for Health Statistics contain information about all cancer deaths in the U.S. The computation of rates for both incidence and mortality is based on population estimates, which are available for every county from the U.S. Census Bureau or state sources (64).

American Indians

Cancer incidence and/or mortality among American Indians has been determined for the time periods 1950–1969 (37) and 1973–1977 (64), using the data sources described above. In addition, total mortality among Indians has been determined for 1960 (28) and 1969–1971 (58). Indians provide an example of a partially low-risk population within the U.S., because they apparently have a relatively low cancer rate and a relatively high total mortality rate.

Geographically Defined Populations

U.S. Cancer Mortality by County and State

U.S. counties have been examined with respect to extreme death rates (49). In a major study of all 3,056 counties and 48 states in the contiguous United States, cancer mortality among white and nonwhite populations was examined during 1950–1969 (35–37). State death certificates listing cancer as the cause of death provided the data base. Each death was ascribed to the county of usual residence as stated on the death certificate. For each county the average annual age-adjusted mortality rates for whites and for nonwhites, for men and for women, was calculated by the direct method, utilizing the total 1960 U.S. population as the standard. County and state populations were taken from the 1950, 1960, and 1970 census, and intercensal estimates were derived by linear interpolation. Data on selected low-risk counties and states are presented in the tables (6,35,64). The extremely low cancer mortality rate of Baldwin County, Georgia is actually incorrect because the institutionalized persons at the Milldegeville State Mental Hospital were included as residents of this county in the census, whereas their deaths were assigned to the usual county of residence (50). Since a large portion of the adult population of this county is institutionalized, the death rate is artificially low and, consequently, meaningless. This example points out the pitfall of accepting published data uncritically without considering correction factors. Accurate data are presented for Washington County, Utah, which has the lowest total cancer rate for any full low-risk county, with at least 10,000 white noninstitutionalized residents as of April 1, 1960.

U.S. Cancer Mortality by State Economic Area

Death detail tapes from the National Center for Health Statistics for the years 1968–1972 were tabulated by cause of death, race, age, and sex, for the 50 states and 510 state economic areas (SEAs) as defined by the Bureau of the Census (48).

The population at risk was obtained from the revised Second Count tape of the 1970 Census of Population through the Institute for Behavioral Research, University of Georgia. Deaths were tabulated by 50 categories of the International Classification of Diseases, Eighth Revision. The age-specific rates for males and females were computed using four 10-year age groups from 35 to 74 years. Rates were calculated by place of usual residence.

Special Countries

Sweden has been included because contemporary Swedes enjoy the longest life expectancy of any nationality in the world (63). Sweden is often cited too as a place where people enjoy excellent health and have an excellent health care system. This country provides an example of a full low-risk white population for comparison with U.S. whites.

Japan has been included because of its unusual site-specific low-risk population with high life expectancy. Also, Japan has served as the basis for migrant studies (20,31) and comparisons can be made with Japanese Americans. The data sources for Japanese populations have been described previously.

Mexico has been included to provide an example of a vital statistics system of uncertain quality (63). However, Mexico City was part of an intensive 1962–1964 Inter-American study of 12 major cities, each with an established death registration system, about 2,000 deaths, and a recently held or planned census (42). Deaths were selected for Mexico City residents aged 15 to 74 years. This death information was confirmed and additional demographic and medical history data were gathered in a field inquiry. The assignment of the cause of death was based on hospital records, and surgical and autopsy findings, and the results of laboratory tests and radiological or other examinations were taken into account along with the statement of cause of death on the death certificate. Data for the entire country of Mexico come from the national vital records office and the 1970 national census (63). Tables show that the carefully collected data for Mexico City yield much higher cancer death rates than the less reliable data for Mexico as a whole. This country provides an example of a partial low-risk population in the sense that they are at low risk to cancer but not to total mortality. Also, the true level of cancer risk in Mexico is not accurately known, at least by U.S. medical standards.

CONCLUSIONS

We have attempted to summarize available information on the theoretical and actual observed preventability of cancer with emphasis on examining the major low-risk populations within the U.S. Using the techniques of Higginson (23) and Doll and Peto (4), we have arrived at a minimum theoretical U.S. cancer risk by recording in Table 5 the lowest 10th percentile age-adjusted cancer death rate among all 3,056 U.S. counties during 1950–1969 for 34 major cancer sites as well as for total cancer (36). The absolute lowest rate for most sites is zero, because no deaths

occurred in a number of the smallest counties; consequently, the lowest 10th percentile was chosen as the most meaningful lower limit. Summing the lowest 10th percentile rate for each of the 34 sites yields a total cancer rate that is 49% of the U.S. average rate. As shown in Table 6, this compares with a theoretical minimum rate that ranges from 5 to 23% of a theoretical maximum rate based on site-specific comparisons of international cancer incidence registries (4,23). Obviously the international variation is greater than the U.S. variation. Schneiderman has made an independent estimate that about 33% of all cancer deaths (about 40% of male deaths and 25% of female deaths) are potentially preventable by applying all current knowledge, e.g., eliminating human exposure to known carcinogenic factors like cigarette smoking, high alcohol intake, excess sunlight, and certain occupational and industrial exposures and obtaining optimum medical care (51). Thus, his estimate of the minimum achievable rate is 67% of the national average rate.

In terms of actually observed minimum risk within the U.S. the lowest 10th percentile total cancer rate among 3,056 counties is 71% of the U.S. average, as shown in Table 6. The lowest total cancer rate for a full low-risk county with at least 10,000 white noninstitutionalized residents in 1960 occurs in Washington County, Utah, and the rate is 63% of the U.S. average. The lowest total cancer rate among 510 state economic areas occurs in the Colorado East Central SEA for white men and in the Utah South SEA for white women and the combined rate is 61% of the U.S. average. These data indicate that the lowest observed cancer risk within the U.S. is not as low as the theoretical predictions based on international or national site-specific comparisons, but is somewhat lower than an estimated minimum achievable risk of 67% (51).

The observed minimum risk among typical nonsmoking populations within the U.S. is also summarized in Table 6. Nationally representative U.S. whites who have never smoked cigarettes have a total cancer risk that is 75% of the U.S. average. This risk is in good agreement with past estimates of the amount of cancer directly attributable to cigarette smoking (4,8,24,51). For representative middle-aged never smokers (ages 35–64 years), the total cancer risk is only 67% of the U.S. average.

Especially healthy cohorts of questionnaire respondents who never smoked, such as the ACS and U.S. veteran cohorts, have a total cancer risk about 66% of the U.S. average. Healthy nonsmoking members of religious groups, such as active Mormons and SDAs, have a total cancer risk of about 60% for all ages and about 50% for ages 35 to 64 years, relative to the U.S. average. These constitute the minimum total cancer risks observed among full-low-risk populations in the U.S. The lower risk among these especially healthy nonsmokers relative to typical U.S. nonsmokers is most likely due to certain healthy selection factors. All are above average in socioeconomic status and education; all except the Mormons are questionnaire respondents; all except the U.S. veterans are known to be health conscious; the Mormons and SDA consume little alcohol or caffeine and practice dietary moderation. Precisely how much of the lower risk is due to each of these or other factors is not known at this time, but is the subject of ongoing research. Further,

TABLE 5. *1950–1969 average annual age-adjusted cancer mortality rates (deaths/100,000) in the lowest tenth percentile of U.S. counties compared with U.S. average*

		Age-adjusted death rates			
		White males		White females	
Cancer site	ICD, 6th revision	U.S. average	Lowest 10th percentile	U.S. average	Lowest 10th percentile
Lip	140	0.33	0.15	0.03	0.00
Salivary glands	142	0.44	0.20	0.22	0.08
Nasopharynx	146	0.38	0.12	0.12	0.00
Tongue, mouth, mesopharynx, and unspecified pharynx	141, 143, 144, 145, 148	4.21	2.10	1.05	0.58
Esophagus	150	4.10	1.78	1.03	0.52
Stomach	151	15.22	8.08	7.70	3.62
Large intestine	153	16.54	6.88	16.25	8.01
Rectum	154	7.65	1.44	4.82	0.97
Biliary passages and liver	155	5.16	2.02	5.34	2.30
Pancreas	157	9.63	5.17	5.83	2.64
Nose, nasal cavities, middle ear and accessory sinuses	160	0.43	0.24	0.23	0.08
Larynx	161	2.54	1.21	0.24	0.06
Trachea, bronchus and lung	162, 163	37.98	17.46	6.29	2.34
Breast	170	0.28	0.10	25.51	13.40
Cervix uteri	171			7.79	3.14
Corpus uteri	172, 173, 174			6.13	2.90
Ovary	175			8.57	3.46
Prostate	177	17.84	12.16		
Testis	178	0.83	0.44		
Kidney	180	3.86	0.93	1.99	0.00
Bladder	181	6.78	1.70	2.39	0.00
Skin melanoma	190	1.55	0.93	1.11	0.73
Other skin	191	1.51	0.99	0.71	0.41
Eye	192	0.23	0.08	0.19	0.00
Brain and nervous system	193	4.42	1.64	2.91	0.51
Thyroid gland	194	0.43	0.16	0.69	0.33
Other endocrine glands	195	0.31	0.09	0.20	0.00
Bone	196	1.35	0.93	0.85	0.53
Connective tissue	197	0.65	0.32	0.48	0.22
Hodgkin's disease	201	2.29	1.59	1.32	0.77
Lymphosarcoma and reticulosarcoma	200, 202, 205	4.89	3.32	3.25	2.06
Multiple myeloma	203	1.76	1.13	1.24	0.80
Leukemia	204	8.81	7.31	5.74	4.68
Others not listed and unspecified sites		12.64	6.01	9.89	5.54
Sum of individual sites	140–205	174.04	86.68	130.10	60.68
All malignant neoplasms combined	104–205	174.04	120.68	130.10	95.71

TABLE 6. *Summary of theoretical and observed minimum risk ratios associated with preventability of cancer*

Description of cancer rate comparison	Geographic area	Time period	Races	Ages (years)	Outcome measure	Minimum risk ratios (%) Males	Females	Both sexes	References
Theoretical minimum cancer risk									
Sum of lowest site-specific rates divided by sum of highest site-specific rates	34 international registries	~1960	All	All	IR	3	6	5	(23)
Lowest total rate divided by highest total rate (approximately Connecticut rate)	34 international registries	~1960	All	All	IR	19	27	23	(23)
Sum of lowest site-specific rates divided by Connecticut total rate	78 international registries	1968–72	All	35–64	IR	20	23	21	(4)
Sum of lowest 10th percentile site-specific rates divided by average total rate	3056 U.S. counties	1950–69	White	All	MR	50	47	49	(36)
Estimated minimum achievable proportion of total rate based on all available knowledge about cancer prevention	U.S.	1976	All	All	MR	~60	~75	~67	(51)
Observed minimum cancer risk									
Lowest 10th percentile total rate divided by average total rate	3056 U.S. counties	1950–69	White	All	MR	69	73	71	(36)
Lowest total rate for a full low-risk county with at least 10,000 white noninstitutionalized residents in 1960, divided by average total rate	~2000 U.S. counties	1950–69	White	All	MR	57	70	63	(35)
Lowest total rate divided by average total rate	510 U.S. SEA	1968-72	White	35–74	MR	59	63	61	(48)
Representative never smokers	U.S.	1966–68	White	35–84	MR	65	86	75	Table 2
Representative middle aged never smokers	U.S.	1966–68	White	35–64	MR	57	78	67	Table 2
Healthy nonsmoking questionnaire respondents		~1960		35+	MR	~50	~82	~66	Table 2
Healthy nonsmoking religious groups		~1970		35+	MR	~50	~70	~60	Table 2
Healthy nonsmoking middle aged religious groups		~1970		35–64	MR	~35	~65	~50	(7,41)

it is possible that even lower risk can be identified among subgroups of these already low-risk populations. However, based on existing published data, we estimate that, relative to the national average, the minimum observed cancer risk in the U.S. is about 50% (35% for men and 65% for women) for middle-aged Americans and about 60% (50% for men and nearly 70% for women) for all American adults.

The minimum risk within the U.S. associated with 34 individual cancer sites is shown in Table 5, although these site-specific low rates are not necessarily associated with low total cancer rates or low total death rates. In general, the lowest rate is about half the average rate for each site, although the ratio varies widely. Among the low-risk white populations described in this chapter, the minimum risk for the five major sites in Table 4 is about 20% for lung cancer, 50% for colorectal and pancreatic cancer, and 80% for prostate and breast cancer. For the nonwhite populations, the minimum risk is quite low for a number of sites, although the total cancer rate is not so low.

The actual preventability of cancer remains to be demonstrated. There is certainly an overwhelming amount of evidence pointing to the benefits of being a nonsmoker. However, the precise effects of smoking cessation on current smokers in the general population are still unknown. One major study showed that British physicians, who reduced their cigarette smoking as a whole by more than 50% over a 20-year period, experienced a reduction in their lung cancer SMR relative to the general British population from 65 in 1955 to 35 in 1972 (4). In a similar study, California physicians, who reduced their cigarette smoking by more than 75% over a 30-year period, experienced a reduction in their lung cancer SMR relative to U.S. white males from 62 during 1950–1959, to 30 during 1970–1979 (10a). These natural experiments provide strong evidence for the benefits of smoking cessation, but they are not rigorous controlled trials. However, two recent randomized controlled trials involving smoking cessation among high risk middle-aged men surprisingly showed no significant difference in total cancer or total mortality rate between intervention group and control group after 7 to 10 years of follow-up (39a,47a).

In view of these data, it is important both to realize the benefits of not smoking and to ascertain what additional factors account for the low cancer mortality experience among various low-risk populations, and to discover how to apply these findings to persons at higher risk of cancer. Some carcinogens that have been given a great deal of attention by the media in recent years are not likely to have an important effect on cancer mortality. These factors include hair dyes, food coloring, saccharin, menopausal estrogens, and low-level ionizing radiation, and various animal and laboratory carcinogens. Even if these factors caused most of the types of cancer with which they have been most strongly linked—primarily cancers of the bladder and endometrium and childhood leukemia—they would have little impact on total cancer mortality. This is because cancers of the bladder and endometrium and childhood leukemia comprise less than 4% of all cancer deaths. As of now, there is no good evidence that the above factors have caused an increase in the cancer death rate in the general population.

One must keep in mind the fact that since 1940 the overall age-adjusted cancer incidence and mortality rates have remained essentially constant, and if lung cancer related to cigarette smoking is excluded then the remaining cancer rate is declining slowly (4). Furthermore, the age-adjusted total mortality rate since 1940 has declined by more than 30% for men and more than 50% for women. Since 1940 the life expectancy of 35-year-olds in the U.S. has increased by 4 years for men and 7 years for women (8).

For the purposes of effective cancer prevention, it is imperative that research be directed first and foremost at factors likely to have the greatest impact on cancer mortality. These factors appear to include personal health habits, diet, socioeconomic status, and certain host factors related to the aging process. The potential for understanding the factors that promote lower risk exists if sufficiently large healthy populations that exhibit lower risk can be found and studied. A substantial degree of cancer prevention could be achieved if higher risk persons would apply this information about low risk to their own personal life-styles.

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