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Quantitative assessment of cancer risk

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Cancer is second only to heart disease as a leading cause of death among Americans. This paper focuses on quantitative risk assessment for two of the top death-causing cancers, lung and breast, and for melanoma and head and neck cancer, all of which have well-understood risk factors. Quantitative approaches to cancer risk assessment can substantially improve physician and patient compliance with cancer prevention measures. These approaches are helpful in identifying extremely high-risk individuals who may require more intensified cancer prevention approaches or modified screening programs. Through quantitative approaches, doctors' and the public's awareness of the general guidelines for cancer screening also is increased. Using data from large cohort studies (giving "relative risks") and case-control studies (giving "odd-ratios"), quantitative approaches focus on well-established avoidable causes of cancer. Besides helping individuals to prevent cancer, quantitative risk evaluations are used to establish attributable risk data which help greatly in the planning of strategies and interventions for population cancer prevention.

KEY WORDS: CANCER RISK, QUANTITATIVE ASSESSMENT, RELATIVE RISK, ODDS-RATIO, ATTRIBUTABLE RISK.

C ancer is the second-leading cause of death in this country. Only heart disease kills more people (1). Over the past 50 years, cancer mortality has increased approximately 250%, and current estimates are that one of every three Americans will develop cancer during his or her lifetime. Of course, cancer is not a homogeneous entity. The Surveillance, Epidemiology and End Results (SEER) report of the National Cancer Institute (NCI) described more than 1,300 cancer subtypes. Despite this diversity, a limited number of tumors impose the major part of the public health burden. Only two histologic subtypes—squamous cell carcinoma and adenocarcinoma of the lung, colon, breast, and prostate—account for 50% of all cancers in the US. Only 15 tumor subtypes account for 80% of all reported cases (2). This article focuses on lung and breast cancer (two of the top death-causing cancers) and on melanoma and head and neck cancer, all of which have well-understood risk factors.

Lung cancer, the leading cause of cancer mortality in the US, increased dramatically over the past 20 years in both males and females. The increasing incidence of this disease adds to its tremendously negative impact on the public's general health and financial condition. Data from the National Cancer Institute SEER program led to the estimates that 152,000 new lung cancer cases and 139,000 lung cancer deaths would occur in 1988 (1).

Breast cancer is the most common type of cancer afflicting females in the US. It is also second in cancer-caused mortality among females, surpassed only recently by lung cancer. Current estimates indicate that one of every ten females in the US will get breast cancer by age 75, and the incidence has been increasing over the past three years by a rate of 1% per year. SEER program estimates are that 135,000 women in the US will develop invasive breast cancer and 42,000 US women will die from this disease in 1988 alone (1).

Head and neck carcinoma accounted for more than 40,000 new cases and 13,000 deaths in 1986, and the incidence of this disease is increasing also. Epidemiologic data indicate that the increasing incidence of this malignancy is due to exogenous factors, such as the use of alcohol and tobacco, which are major independent and synergistic risk factors (3). The increasing use of smokeless tobacco by younger people in the US has raised the frequency of oral cancer in this group.

In 1988, US estimates are that new cases of and deaths from melanoma will be 27,000 and 6,000, respectively (1). This malignancy is especially drug-resistant and increasing in incidence. It is an increasing major problem in the South.

Risk data for colorectal cancer are less well developed (1), but the SEER report estimated that there would be 147,000 new cases of colorectal cancer in 1988 and that 62,000 people would die from it in that year. It is known, for example, that having a first-degree relative with colon cancer increases one's risk of colon cancer by two to four times, but the identification of specific high-risk groups (eg, persons with familial polyposis or nonpolyposis syndromes or ulcerative colitis) has not been worked out (4). Possibly, some of the current prospective dietary studies at the Arizona Cancer Center and elsewhere regarding fat and fiber will yield helpful quantitative data.

The US picture is improving for gastric carcinoma and cervical carcinoma. Unfortunately, we can only guess why the incidence of gastric carcinoma is decreasing. Although the incidence of cervical carcinoma remains unchanged, its mortality rate has decreased significantly due to screening (Pap smears). Advances in chemotherapy have improved survival in some uncommon malignancies, such as testicular cancer and certain lymphomas and leukemias, but chemotherapy has not significantly improved survival for the major death-causing cancers in this country, including lung, breast, and colorectal cancers. Therefore, until more effective standard therapies are developed, primary prevention and screening are the only chances to reduce mortality from these malignancies.

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American Cancer Society, (ACS) now are urging improvements in primary prevention and screening measures (5). Primary prevention is the avoidance of exposure to carcinogens in order to prevent the occurrence of carcinomas (eg, smoking cessation to prevent lung cancer). Screening (eg, Pap smears and mammography) does not deter the occurrence of carcinomas or precancerous conditions, but detects them early and therefore markedly increases the chances of cure. Other preventive approaches include drug intervention (eg, tamoxifen citrate in women at high risk for breast cancer) and adjuvant therapy (6). Although important, these complex issues are not a part of the present discussion.

A quantitative, or objective, approach to cancer risk assessment will be a major step toward improving physician and patient compliance with cancer prevention measures. Nonquantitative, or subjective, approaches can be counterproductive and lead to unwarranted cancer fears among some people at lower risk (eg, the niece of a woman with postmenopausal breast cancer) and unwarranted fatalism among some individuals with extremely high cancer risks who may decide erroneously that it is "too late to change" (eg, heavy smokers and alcohol drinkers). Subjective approaches tend to promote the specious attitude that "everything causes cancer." Actually, there are only a few well-established human carcinogens. Aside from alcohol, asbestos, sunlight, and tobacco, most carcinogens are compounds such as chemotherapeutic agents and irradiation that only affect select populations (7).

The bottleneck in cancer prevention and screening compliance appears to be at the level of the primary care physician (8,9). Studies demonstrate that patients are very responsive to and generally comply with their physicians' advice regarding cancer prevention (9). Therefore, physicians must become far more familiar with quantitative data regarding cancer risk assessment in order to better advise patients on primary prevention and screening measures. As former NCI Director Vincent T. DeVita, Jr, MD, stated in 1985, "We are missing the boat if we do not make active attempts to counsel patients about the way they can reduce their [cancer] risk" (9). This article discusses the well-established risk factors for melanoma and carcinoma of the lung, breast, and head and neck. Understanding of these risk factors facilitates identification of patients at high risk of developing these malignancies and allows for more definitive recommendations regarding cancer prevention and screening.

Epidemiologic quantitative techniques

The language of epidemiologists, who have quantitated the relative risks for developing many cancers, is quite specialized (10). The following important epidemiologic terms must be defined for a full

understanding of quantitative cancer risk assessment: cohort study, case-control study, incidence or incidence rate, relative risk, odds-ratio, and attributable risk.

The terms *cohort* and *case-control* apply to the two analytic designs of epidemiologic studies and describe two types of population groups. Cohort studies involve subject populations first identified by exposure to carcinogens and followed prospectively to evaluate the cancer risk by determining how many exposed subjects develop cancer. Case-control studies involve subjects first identified by their disease and then studied retrospectively to try to determine what exposures led to the development of their cancers.

Epidemiology studies rely on the important measure of *incidence*, or *incidence rate*, which is defined as the rate at which a disease occurs in a specific group over a specified period of time. In a cohort study, the incidence rate is used to determine the *relative risk*, which is the key term used by epidemiologists in quantitative cancer risk assessment.

Relative risk is expressed as an absolute number. A smoker's relative risk for developing lung cancer, for example, is *10*. This means that the smoker is at ten times greater risk of getting the disease than is a nonsmoker. Therefore, a relative risk of 1.0 indicates no increased risk over that of the nonexposed person, and a relative risk of less than 1.0 indicates a protective effect from exposure to a substance.

In a case-control study, the incidence rate cannot be calculated precisely, and so cancer risk must be derived from formulas and tables that determine the *odds-ratio*, or estimated relative risk, for people who have certain predisposing factors (eg, carcinogen exposure and genetic factors). Unfortunately, much of the data for cancer risk assessment is based on these inexact evaluations made from case-control studies. Although requiring greater expense in time and funds, it is hoped that more cohort studies will be conducted in the future so that more precise incidence rates and relative cancer risks can be determined for the carcinogens and genetic factors predicting America's major lethal cancers.

Attributable risk is another important term to understand because it differentiates between a factor's high relative risk and its overall contribution to the incidence of cancer in the general population (11). For example, radon exposure has the extremely high relative risk for lung cancer of 20, but due to the tiny number of exposed individuals, its attributable risk in the total population of lung cancer patients in this country is only 10%. On the other hand, smoking, with a smaller relative risk of 10, has an attributable risk of more than 80% due to the enormous percentage of the lung cancer population who smoke (2). Therefore, attributable risk is

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an important consideration when planning strategies for population cancer prevention interventions.

Breast cancer

The importance of screening for breast carcinoma is demonstrated by results from routine cancer screening with mammography in women who are over the age of 50. Several large, prospective randomized studies have shown that mammographic screening reduces breast cancer mortality by 30% to 50% (12). Although numerous, most breast cancer risk factors are small, indirect, and not amenable to primary prevention (2,13). Therefore, the reduction of breast cancer mortality will have to rely on screening measures. Minor breast cancer risk factors include education level, race, weight, religion, marital status, socioeconomic status, age at menarche, age at natural menopause, bilateral oophorectomy, first-trimester abortion before first full-term pregnancy, age at first pregnancy, nulliparity, benign breast disease, family history, radiation, and moderate alcohol consumption. The major risk factor is age. Eighty-five percent of all breast cancer is detected in women who are more than 40 years old, and 67% of breast cancer cases occur after age 50 (1). (This explains why screening studies have detected the most significant decreases of breast cancer mortality in women over age 50.) Fewer than 1.5% of all breast cancer cases are diagnosed in women under 30 years old. Unfortunately, it is unclear whether most of these risk factors are independent or dependent variables or how they may interact. A patient with several different breast cancer risk factors ranked in the relative risk range of 1 to 3 could still have an absolute relative risk of only 3. This characteristic differs markedly from the well known interactions between other malignancies' risk factors, such as tobacco, asbestos, and alcohol, which are known to act synergistically and dramatically increase the absolute relative risk.

In ascending order of importance, the three most significant risk factors for breast cancer, other than age, that can be quantitated for relative risk are (a) age at first pregnancy, (b) benign breast disease, and (c) family history. A clear direct relationship exists between a woman's risk of breast cancer development and her age at first full-term pregnancy (14). From 20 years old or younger to 35 years old or older, the risk increases progressively (relative risk of 1.0 to 2.7). Greatest of all is the risk for women with first pregnancy after age 35 or nulliparous women. This risk is additive with family history. For example, risk factors of a full-term pregnancy in a woman 30 years old or older and a first-degree relative with breast cancer are associated with a combined relative risk of 5.6 (14). Overall, benign breast disease is reported to impart a relative risk of between 2 and 3 (13–15). In a recent

elegant study, however, DuPont et al (15) showed that proliferative lesions (especially those with atypical hyperplasia) were the primary histologic subtypes of benign breast disease associated with increased breast cancer risk. Women with benign breast tumors having atypical hyperplasia have a relative risk of 4.4, which jumps to 8.9 when women with these tumors also have a family history of breast carcinoma.

Genetic/familial risk factors for breast cancer are of major importance and concern for women in this country. Three classic studies have addressed this issue—two population-based studies (16,17) and one large clinic-based study from The University of Texas MD Anderson Cancer Center (18). Ottman et al (16) conducted one of the population-based studies and identified two high-risk groups. One group included women whose 60% breast cancer risk by age 60 and a 99.9% breast cancer risk by age 70 were associated with having sisters with bilateral breast carcinoma diagnosed before age 40. The second Ottman group included women whose 25% to 30% breast cancer risk by age 60 was associated with a sister having bilateral breast cancer diagnosed between ages 41 and 50. In this and some other studies, sisters of breast cancer patients had greater risk than mothers of breast cancer patients. Although this makes no sense genetically, the increased risk in sisters may be due to the significant percentage of nulliparous sisters, since nulliparity is a significant independent risk factor. Reported by Schwartz et al (17), the second population-based study also identified two high-risk groups. One group consisted of women whose 18% probability of developing breast cancer by age 50 was associated with having a sister with breast carcinoma diagnosed before age 40. The second Schwartz group consisted of women whose 54% probability of developing breast cancer by age 65 was associated with having both a mother and a sister diagnosed with breast cancer. The large clinic-based study from MD Anderson (18) differs from the two population-based studies in several ways, but especially in respect to ascertainment bias. In this study, the two high-risk groups were (a) women with a sister having bilateral disease and a mother with breast cancer and (b) women with a sister having bilateral disease and another sister with breast cancer. Women in both groups had a 25% to 30% probability of developing breast cancer by age 70.

In summary, all of these studies demonstrate that women with the following characteristics are at very high risk of developing breast cancer (greater than 50% cumulative [lifetime] incidence): (a) benign breast disease with the histology of atypical hyperplasia and a first-degree relative with breast cancer, (b) two or more first-degree relatives with breast cancer, and (c) a first-degree relative with bi-

lateral breast cancer diagnosed before age 50 or, especially, before age 40. Doctors must understand in a quantitative way the factors imparting extremely high risks so that they can appropriately discuss cancer prevention and screening measures with female patients. This quantitative knowledge of risk factors is needed also for proper counseling in respect to selective screening, prophylactic bilateral mastectomy, and drug intervention, which are not further discussed in this article.

Aerodigestive tract cancer (lung, head and neck, and esophageal cancer)

CIGARETTES

For the tobacco industry, the good news is that smoking does appear to reduce the risk for one particular type of cancer—endometrial cancer (19). Unfortunately, this reduction may be due to smoking-caused onset of early menopause. The bad news is that in addition to being a major risk factor for heart and lung disease, a survey from 1980 estimated that smoking accounted for 76% of lung cancer, 24% of cervix cancer, 26% of pancreas cancer, 29% of bladder cancer, and 74% of laryngeal and esophageal cancer cases (2).

Five major factors can influence the cancer risk in smokers: number of cigarettes smoked per day, use of filter versus nonfilter cigarettes, age when the individual began smoking, duration of smoking habit, and number of years since the patient stopped smoking (20,21). A clear dose-response relationship exists between lung cancer and the number of cigarettes smoked per day (20). People who smoke 1 to 9 cigarettes per day have a lung cancer relative risk of 4 to 5, whereas people who smoke more than 40 cigarettes per day have a relative risk of 20 (21). The use of filter cigarettes appears to reduce one's risk of lung cancer by approximately 25%. The age one begins smoking is also a major risk factor. People who began smoking when they are less than 15 years old have a relative risk of 15, whereas those who began after age 25 have a relative risk of 3.2 (21).

Unequivocally, the major risk factor for lung cancer is the duration of smoking. Doll and Peto (22) have shown that although a threefold increase in the number of cigarettes per day results in a threefold increase in cancer-causing effect, a threefold increase in duration was associated with a 100-fold increase in lung cancer incidence! Therefore, although the term "40 pack-years" applies either to someone who smoked two packs per day for 20 years or someone who smoked one pack per day for 40 years, clearly the person smoking one pack per day for 40 years has a much greater cancer risk. Despite its importance, a remarkably sparse amount of cohort data on smoking duration is available.

The beneficial effect of stopping smoking has been well documented (20–22). This is an extremely important fact to know in counseling patients who feel that "it's too late to stop." In moderate smokers (fewer than 19 cigarettes per day), it has been shown that stopping smoking for five years reduces the relative risk to near 1.0. Heavy smokers (more than 20 cigarettes per day) must stop for ten years to reduce their lung cancer relative risk to near 1.0. Stopping smoking for more than six years results in a 50% decrease in laryngeal cancer risk, and stopping for over 16 years results in a 70% decrease in laryngeal cancer risk (21). It is important to realize that the decrease in relative risk is slower and less complete in heavy smokers than in lighter smokers. (These patterns also have been well documented for smoking cessation and reduced heart disease risk.) The lung cancer relative risk relates primarily to squamous cell histology. People smoking more than 50 years have a squamous cell carcinoma relative risk of 42 and an adenocarcinoma relative risk of only 5.7 (21).

SMOKELESS TOBACCO

The use of smokeless tobacco (chewing tobacco and snuff) is a major problem in young people in this country, especially in the southern states, and is associated with the following relative risks in men: laryngeal carcinoma, 1.8; pharyngeal carcinoma, 1.9; and oral cavity cancer, 7.1 (23). Winn et al (24) studied the risk to white women in the South who used snuff. They reported that snuff use by nonsmoking women resulted in a relative risk of 4.2 for oral cancer. A remarkable finding from Winn's study was that prolonged use of snuff markedly increased the relative risk for developing oral cancer. White southern women who had used snuff for over 50 years had a relative risk for gum and buccal mucosa cancer of nearly 50! In contrast to the risk of oral cancer, no significant increase in relative risk of pharyngeal cancer among women exposed to prolonged (more than 50 years) snuff use was observed by the Winn group.

CIGARS AND PIPES

The use of pipes alone is associated with a relative risk of 2 to 3 for lung cancer (25). Cigar use alone is associated with a relative risk of 3 for lung cancer and a relative risk of 4 (25) for laryngeal cancer. A definite dose-response relationship exists between cigar and pipe smoking and lung cancer (23,25). People smoking more than seven cigars or more than 6 g of pipe tobacco per day have a lung cancer relative risk of approximately 9.0 (25). Duration also has an effect on cancer risk. In addition to increasing risk of lung cancer, pipes and cigars appear to increase the risk for oral, laryngeal, pharyngeal, and esophageal cancer.

ASBESTOS

Although improvements in certain business and work practices have markedly decreased exposure to asbestos dust over the past 20 years, asbestos dust is still probably the most significant established environmental and occupational human carcinogen. In 1981 approximately 2.5 million workers, or 1.1% of the US population, were exposed to asbestos. Asbestos exposure for more than 20 years results in the following relative risks: all cancer, 3.1; lung cancer, 4.9; esophageal cancer, 3.3; pancreatic cancer, 2.9; laryngeal/pharyngeal cancer 2.8; and mesothelioma, 100 (26). The important aspect of synergy between asbestos exposure and cigarette smoking in causing lung cancer is discussed below.

ALCOHOL

Alcohol is not a major independent cancer risk factor (27). As with asbestos, its major contribution to the carcinogenic process is its ability to potentiate tobacco's cancer-causing effect.

SYNERGISTIC CARCINOGENS

Asbestos exposure clearly acts synergistically with cigarette smoking in causing lung cancer (26). Cigarette smoking is associated with an overall lung cancer relative risk of 10. People who have been exposed to asbestos for more than 20 years and currently smoke cigarettes have a lung cancer relative risk of 53. More precisely, people with 20 years of asbestos exposure who smoke less than 20 cigarettes per day have a relative risk for lung cancer of 51. People with a similar exposure history who smoke more than 20 cigarettes per day have a relative risk of over 85 (26).

Synergy between alcohol and cigarettes has been well documented for the occurrence of oral carcinoma, laryngeal carcinoma, and esophageal carcinoma (21,27). Heavy drinkers have an oral cancer relative risk of 2. Heavy smokers have a relative risk of 2.5 for oral cancer. However, people who are both heavy smokers and heavy drinkers have a relative risk of over 15 for oral carcinoma (28). Similar synergistic findings have been reported for laryngeal carcinoma, the relative risk of which is more than 30 for heavy drinkers and heavy smokers (29). In one study, heavy smokers and heavy drinkers had a relative risk of over 150 for esophageal carcinoma (30)! Although difficult to quantitate accurately, radiation exposure appears to potentiate lung cancer risk in smokers. This was shown in a study of uranium miners (31). Miners with heavy radiation exposure and a 30-pack-year smoking history had a lung cancer relative risk of nearly 150.

Melanoma

Melanoma is a major public health problem, especially in the southwestern US. There is no effective therapy for advanced disease, and at present the only effective way to reduce melanoma mortality is through primary prevention and early detection of high-risk patients. The major melanoma risk factor is the presence of its precursor lesion, the dysplastic nevus (relative risk more than 50), especially in melanoma-prone families with a history of melanoma (relative risk 500) and those without a previous melanoma (relative risk approximately 150) (32). The following risk factors are widely accepted and have been quantitated from patient self-reporting studies (33): (a) the estimated number of moles on the body, (b) predisposition to freckling, (c) hair color, (d) eye color, (e) skin color, (f) previous skin cancers, (g) prolonged sunburns (especially in childhood), (h) inability to tan, (i) occupation, (j) duration and timing of sunlight (outdoor) exposure, (k) geographic location, and (l) first-degree relatives with melanoma.

Future directions

Many cancers, including advanced stages of the major killers (lung, colon, and breast cancer) do not respond significantly to therapy. Therefore, the numbers are relatively simple: increased compliance with cancer prevention and screening measures will save many lives now lost to advanced disease.

Compliance with these measures will certainly improve with the broad dissemination of concise information about cancer risk. Already epidemiologists have made great strides in ascertaining and quantitating relative risks for various cancers, including the major killers. Their research, including biochemical and molecular epidemiologic investigations (34,35), must continue to develop new data on relative risks so that primary prevention and selective screening measures can be increasingly effective in targeting the highest-risk groups.

Multifaceted programs (educational resources, genetic evaluation, quantitative risk assessment questionnaires, and prevention and control clinics), such as those at the MD Anderson Cancer Center and the Arizona Cancer Center, are designed to promote quantitative cancer risk assessment made through the use of the painstaking epidemiologic data. This approach will help the physician and patient develop an objective lifelong cancer prevention strategy that eliminates problems, such as unwarranted fears, associated with the subjective perception of cancer risk (36).

Our goal and that of the NIH, NCI, and ACS is not only to help individuals today, but to spread the message to physicians and the population at large that prevention and screening are essential tools along with advanced therapeutic approaches in the fight against cancer (5,37,38). We hope that more community and university medical centers will

want to develop similar programs. With education, objective quantitative risk assessment, and clinical compliance in prevention and screening, cancer mortality is destined for a significant decline.

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EDITOR'S NOTE:

A table of selected information from this article is available from Dr Lippman.