Carcinogenesis vol.18 no.1 pp.97–105, 1997

Avoided and avoidable risks of cancer

Lorenzo Tomatis[1,7], James Huff[1,8], Irva Hertz-Picciotto[2], Dale P.Sandler[1], John Bucher[1], Paolo Boffetta[3], Olav Axelson[4], Aaron Blair[5], Jack Taylor[1], Leslie Stayner[6] and J.Carl Barrett[1]

[1]National Institute of Environmental Health Sciences, PO Box 12233, Research Triangle Park, NC 27709–2233, USA; [2]School of Public Health, Division of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [3]International Agency for Research on Cancer, 69372 Lyon, Cedex 08, France; [4]Department of Occupational Health, Universitet Linkoping, S-58183 Linkoping, Sweden; [5]National Cancer Institute, Environmental Epidemiology Branch, 6130 Executive Blvd., MSC 7364, Bethesda, MD 20892–7364, USA; [6]National Institute of Occupational Safety and Health, Cincinnati, OH, USA

[7]NIEHS International Scholar on Environmental Health. Permanent address: Istituto per l'Infanzia, Via dell'Istria 65/1, 34137 Trieste, Italy

[8]To whom correspondence should be addressed

Despite the considerable efforts and funds devoted to cancer research over several decades, cancer still remains a mainly lethal disease. Cancer incidence and mortality have not declined at the same rate as other major causes of death, indicating that primary prevention remains a most valuable approach to decrease mortality. There is general agreement that environmental exposures are variously involved in the causation of the majority of cancer cases and that at least half of all cancers could be avoided by applying existing etiologic knowledge. There is disagreement, however, regarding the proportion of cancer risks attributable to specific etiological factors, including diet, occupation and pollution. Estimates of attributable risks are largely based today on unverified assumptions and the calculation of attributable risks involves taking very unequal evidence of various types of factors and treating them equally. Effective primary prevention resulting in a reduction of cancer risk can be obtained by: (i) a reduction in the number of carcinogens to which humans are exposed; or (ii) a reduction of the exposure levels to carcinogens. Exposure levels that could be seen as sufficiently low when based on single agents, may actually not be safe in the context of the many other concomitant carcinogenic and mutagenic exposures. The list of human carcinogens and of their target organs might be quite different if: (i) epidemiological data were available for a larger proportion of human exposures for which there is experimental evidence of carcinogenicity; (ii) more attention was paid to epidemiological evidence that is suggestive of an exposure-cancer association, but is less than sufficient, particularly in identifying target organs; and (iii) experimental evidence of carcinogenicity, supported by mechanistic considerations, were more fully accepted as predictions of human risk.

Introduction

The aim of primary prevention is to reduce mortality and disability by reducing the incidence of disease. The role of primary prevention is of particular relevance for lethal diseases like cancer, where reductions in mortality are largely achieved through a reduction in incidence. Public health programs to prevent diseases have a long and successful history. Primary prevention of non-malignant diseases (e.g. infectious diseases, silicosis) have been generally easier to document and evaluate than cancer prevention programs. Even in cases where intervention strategies for cancer prevention are highly effective, such as in occupational settings, these have not always been accurately documented (1,2).

Primary prevention of human cancer can be accomplished in two ways: (i) avoiding the introduction of carcinogenic agents into the environment; and (ii) eliminating or drastically reducing exposure to carcinogenic agents that are already in our environment. The first approach can be most effectively implemented by identifying carcinogenic substances before they are introduced into the environment in any sizeable amount (3). Although theoretically effective, it is difficult, if not impossible, to quantify precisely how much primary prevention has been or can be achieved by such measures.

The second approach involves actions aimed at reducing or eliminating occupational or other exposures to carcinogens. Suitable examples are the disappearance of an occupation where a carcinogenic exposure occurs, such as that of mule-spinners in cotton mills in England or banning the production and use of carcinogenic chemicals such as certain aromatic amines (3), and the regulatory standards set by the Occupational Safety and Health administration (OSHA) aimed at reducing exposures to carcinogens in the workplace and general environment. However, some argue that primary prevention efforts aimed at reducing cancer mortality associated with exposures to environmental agents are likely to have little impact on overall mortality and cannot be accurately quantified, especially when either few people are exposed or when environmental exposures are low. Historical experience in eliminating carcinogens, including those in the workplace and tobacco smoking, however, suggests the contrary. The drastic reduction in incidence and mortality for gastric cancer, even if its exact cause(s) have not been precisely identified, is likely due to the elimination of environmental carcinogens and/or the acquisition of protective factors through improved living standards, that include efficient methods for storage and distribution of food.

Although primary prevention of occupational carcinogens must logically result in lowered cancer rates, such reductions are not easily documentable in quantitative terms because most of the published reports on the subject are limited to predicting declines in cancer risk. Such predictions are generally based on assumptions about exposure–response curves and not on actual observations on changes in risk after exposure reduction. Unfortunately there are few follow-up studies designed to determine whether cancer rates actually declined as a result of preventive measures taken. This absence of documentation may reflect disinterest on the part of researchers, lack of funding for studying 'non-events' resulting from successful

prevention, and few opportunities for 'before–after' studies where the only change is the preventive measure taken.

A possible source of information on the effects of intervention are studies of occupational cohorts that include some individuals employed before and others only after changes in exposure have occurred. Unfortunately, it is difficult to identify reductions in mortality or attribute changes to the interventions, because workers hired after intervention will invariably be younger and will have had both fewer years of exposure and a shorter follow-up period. Furthermore, if reducing exposure to an agent leads to protracted latency, an apparent reduction in risk might be overestimated. Conversely, the absence of an apparent reduction in mortality could be due to prior exposures in workers that pre-date the intervention.

A well documented case is that of tobacco smoking. The industrial production of cigarettes began at the middle of the last century (the first cigarette factories opened in Havana, Cuba in 1855, in London, England in 1857 and in Richmond, Virginia in 1863) (4) and expanded, in parallel to the chemical industry, spreading first within the industrialized and then to the developing countries, a trend that continues today. The decreasing risk of cancer in individuals who have quit smoking provides strong evidence that the elimination of exposure results in reduction of risk (5).

Lung cancer rates decrease with exposure reduction (number of cigarettes per day or duration of smoking) and time since stopping smoking (6). Indeed, the decreasing mortality from lung cancer in males from successively younger cohorts in the UK, USA, Finland and possibly other countries is largely, although not exclusively, linked to the decreasing proportion of smokers among the young (7).

To demonstrate that primary prevention of environmentally induced cancer is highly relevant and feasible, we will discuss the following points: (i) cancer incidence and mortality have not declined at the same rate as for other major causes of death, indicating that both primary prevention and advances in cancer treatment are required to decrease mortality; (ii) attributable risks calculated for the entire population, often with a large margin of uncertainty, may influence decisions on priorities for intervention toward changing life styles, which ignore the importance of measures aimed at reducing exposure to environmental agents; (iii) experimental and epidemiological approaches play a complementary role in the identification of human carcinogens; (iv) of dose–response relationships and thresholds may have important implications for primary prevention; and (v) low levels of exposure to multiple carcinogens may seriously impact cancer burden in the general population.

Trends in cancer mortality and incidence

Despite the enormous efforts and funds devoted to cancer research, improvements in cancer survival and incidence have, on the whole, been small (8–11). The emphasis on cancer treatment has also been seen as diverting attention from the identification and control of important non-carcinogenic hazards (12). While mortality from cardiovascular and ischemic heart diseases is decreasing, mortality from cancer is still increasing (13). Progress in cancer therapy, although considerable for certain forms of neoplasia such as Hodgkin's lymphoma, testicular tumors and various childhood cancers, have been as a whole limited. Overall improvements in survival have been relatively modest and are counterbalanced by an increase in incidence for certain sites. In Europe, among men, only four relatively uncommon cancer sites (namely, testis, larynx, penis and Hodgkin's disease), have a 5-year survival $>50\%$. In women the situation is more favorable with eight sites, including breast and cervix, having survival rates $>50\%$ (14).

Analyses of time trends in cancer incidence and mortality have been accompanied by contradictory interpretations (15,16). To a considerable extent the disagreements stem from the different emphasis placed on tobacco-related cancers, and in particular on lung cancer. Changes in lung cancer mortality, however, are not completely explained by changes in tobacco smoking. Based on models aimed at removing the contribution of changes in smoking habits (17,18), it appears that other factors, operating during the same time period as the increase in smoking, may have increased rates of lung cancer, although this effect is largely obscured by the predominance of smokers among persons with lung cancer. Concomitant occupational as well as environmental exposures (e.g. indoor radon exposures) may also have played a role, but the separate contributions of smoking and other factors are difficult to ascertain, especially because exposures may be correlated. For example, smoking may be more common among certain occupational groups whose work exposures may also be carcinogenic.

It is often claimed that in most countries cancer mortality would show a clear downward trend, if it were not for the continuing rise in smoking related lung cancer incidence. Trends in total cancer mortality are dominated by the trends in the most frequent types of cancer. For instance, age-adjusted cancer mortality rates between 1970–1990 in Europe have increased by 8.7% in men and decreased by 1.4% in women. However, without lung cancer, the age-adjusted mortality rate for all other cancers still shows an increase in men of 5.7%, although for women non-lung cancer mortality shows a decrease of 5.4%. If we also exclude stomach cancer, the incidence of which is steadily decreasing, age-adjusted mortality rates for all remaining cancers show an increase between 1970–1990 of 17.6% in men and of 5.2% in women (19).

Conclusions may also depend upon the method used to assess cancer trends (7). Cancer risk is strongly related to age, and cohort effects may lead to apparent trends. Cancer trends may vary across age groups. Following a reduction in an environmental exposure with long latency, rates may decrease in young age groups and still increase in old age groups. Since different measures of cancer occurrence give different weight to the various age groups, they may yield seemingly contradictory results. For instance, the trend in age-adjusted cancer mortality rates truncated at age 64 in two neighboring countries, the USA and Canada, is leveling off among males in the USA but not in Canada, whilst mortality among females is increasing slightly in both countries. On the other hand mortality trends in successive birth-year cohorts point to a decrease in mortality in younger ages of each sex in both countries (7). While obviously encouraging, it is uncertain whether this downward trend will persist with the aging of the cohorts. Trends in USA mortality rates for the years 1973–1991 show a slight decrease among people under 65 but an increase among those aged 65 and over, and the trends in incidence rates show an increase at all ages, more pronounced at ages 65 and over (20–22). An additional worrisome observation is the apparent slight, but continuous, increase in incidence of childhood cancer in industrialized countries (20,22–26).

Cancers showing a strong decline in mortality in most industrialized countries are stomach, endometrial and cervical cancer (7). These trends are largely not explained by therapeutic advances. The decline in cervical cancer mortality is mainly due to screening programs established in many countries and is possibly related to improved hygiene. The reasons for the decrease of stomach and endometrial cancer mortality are not well understood but may be related to socioeconomic improvements and dietary changes for stomach cancer, and for endometrial cancer to a decrease in the therapeutic use of estrogen.

The conclusions drawn from considering trends in cancer incidence and mortality are that: (i) no evidence of declines in incidence or mortality is apparent for cancer as a whole, nor can a decline be predicted for the near future; (ii) efforts and funds spent on improving diagnostic and therapeutic interventions have been successful for some cancers but have had little impact on others; (iii) cancer remains a lethal disease; and (iv) primary prevention is and remains a highly relevant approach to further reduce mortality.

Attributable risks

There is general agreement that at least 50% of all cancer cases could be avoided if existing etiologic knowledge were applied (27–33). There is disagreement, however, regarding the proportion of cancer risks attributable to specific etiological factors, including dietary constituents, occupational exposures and pollution. The multifactorial origin of most tumors makes it particularly difficult to measure the role and to quantify the contribution of single agents. Estimates of attributable risks are largely based on unverified assumptions. Most assessments, therefore, of the percentage of cases that could be avoided by intervening on single factors contain a considerable amount of uncertainty. The proportion of cases attributable to diet in the USA, for instance, has been estimated at between 10 and 70%, with a 'best estimate' of 35% (29). The concept of prevention is further complicated because attributable risk is widely misunderstood to mean the proportion of all cases of the disease that are caused by an individual exposure. It is in fact inappropriate to view the sum total of disease burden as divisible into a set of mutually exclusive subsets, each having a different cause. For any given case of cancer, multiple factors may have operated, thus the sum of all attributable risks may exceed 100%.

Much of the early understanding of the etiology of human cancer originated from studies of occupational groups exposed to high concentrations of chemical carcinogens, the human equivalent to the high dose long-term experimental carcinogenicity tests (34). Many occupational carcinogens can also be found in the general environment where they will not necessarily cease to be carcinogenic when present at lower concentrations than in the working environment. One such example is asbestos (35).

Some authors argue that the role of environmental and occupational carcinogens has been overemphasized and that the majority of cancer cases are explained by life-styles, interpreted as personal choices (36). In this vision, occupational and other unintentional exposures to environmental agents play a minor role because between 20–40% of cancer cases are attributed to dietary factors, at least 35% to tobacco smoke and 5% to alcoholic beverages (16). An earlier assessment of the preventable causes of cancer attributed between 25–40% of cancers to tobacco and 10–70% to diet (29). The key to the prevention of most human cancers has therefore been claimed to be the adoption of lifestyle factors associated with low cancer risks, such as those followed by Seventh-day Adventists (16).

Although tobacco and diet play a relevant role in the occurrence of cancer, the importance of other preventable factors is underemphasized. The weakness of the personal choice argument lies in the fact that the calculation of attributable risks involves taking very unequal evidence for various factors and treating them equally. While conclusive epidemiological studies supporting a causal relationship between an agent and human cancer is usually considered a necessary requirement for declaring an agent carcinogenic to humans, tables of attributable risks are based on circumstantial or less than conclusive epidemiological evidence of a causal relationship. The evidence of causal associations between numerous occupational and environmental agents and cancer is generally strong, whereas the evidence regarding the dietary contribution to cancer burden is mostly circumstantial and in some instances rather weak. Furthermore, the attribution of the majority of cancer cases to lifestyles, interpreted as being mainly related to personal choices, overemphasises the individual's responsibility, drawing attention away from the insufficient commitment and/or the lack of interest of governments toward public health (37).

Identification of human carcinogens

Until the early 1970s, the most authoritative source of information on the causes of human cancer was a World Health Organization report on Prevention of Cancer (38). A tentative list of 16 recognized human carcinogens can be extracted from this report in which atmospheric pollution was considered an important etiologic factor for lung cancer, and commercial benzol was mentioned as a suspected human carcinogen. The relevance of experimental carcinogenesis and long-term carcinogenicity testing was strongly emphasized, with the clear implication that experimental results could serve as a basis for preventive measures.

When in the late 1920s, using a technique developed in Japan (39), tumors of the skin were induced in the mouse with soot extracts (40) the results were greeted as final confirmation of the observations made by Pott a century-and-a-half before of an excess of scrotal cancer among chimney sweeps (41). The implicit recognition of the importance of an experimental confirmation of a clinical observation marked the beginning of an era, which lasted several decades, during which experimental chemical carcinogenesis played a prominent role in cancer research.

In the late 1960s, not long after the publication of the WHO report, the confidence in experimental results for the prediction of human risks began to decline. A severe limitation of the experimental approach in the identification of etiologic factors was that, having elaborated a convincing hypothesis (42,43), adequate methods were not developed for identifying and evaluating the different protagonists in a multistep, multifactorial carcinogenesis process. As a consequence, in spite of wide acceptance of the notion of a multifactorial origin of most tumors, the tendency to search for the origin of cancers attributable to single factors persisted. Confidence in experimental results was additionally undermined by the inability to reproduce in experimental animals the striking epidemiological observations of the carcinogenicity of tobacco smoke in

Table I. Human carcinogens identified by IARC, 1972–1996

Industrial processes	13
Chemicals or chemical mixtures identified in the working environment	20
Medical drugs	25
Cultural habits	5
Biological agents	7
Total	70

Source: IARC, 1972–1996.

humans. In view of these apparent limitations of the experimental approach, epidemiologists and statisticians developed criteria for assessing causation of chronic diseases that included biological plausibility, but relied primarily on epidemiological evidence (44). After the acceptance that epidemiological results could by themselves alone provide evidence of a causal relationship, epidemiological evidence was often considered as the only acceptable proof.

Following the WHO publication (38) the International Agency for Research on Cancer (IARC) has officially recognized, on the basis of epidemiological evidence, 70 agents or exposures as human carcinogens on the sole basis of epidemiological evidence (with the only exception of ethylene oxide) where mechanistic considerations played a determining role (45). Of these, 13 are industrial processes and 20 are chemicals found carcinogenic in the working environment, 25 are medical drugs, five are cultural habits (prominent among which is tobacco smoking), and seven are biological agents (Table II). On the basis of the combined human and experimental data 57 additional chemicals or chemical mixtures are considered by IARC to be probably and 224 possibly carcinogenic to humans. The proportion of chemicals that have entered our environment and have been submitted to chronic toxicity testing remains rather low (46). Although the majority of the untested chemicals are probably not carcinogenic, for the simple reason that those most highly suspected of carcinogenic activity have already been tested, it is likely that some of them may be found carcinogenic (47).

Much of the testing of chemicals for carcinogenicity, is today performed by the US National Toxicology Program (NTP). The criteria for selection of a chemical for study by the NTP include a strong suspicion of carcinogenicity or a large production and widespread human exposure. Analysis of the results of 450 chemicals tested to date, shows that 65% of the chemicals selected on the basis of an *a priori* suspicion of being carcinogenic were in fact carcinogenic, while only 20% of those selected on the basis of exposure criteria were carcinogenic (47). Within the IARC program on the evaluation of the carcinogenic risk to humans, 70 (9%) of the 821 agents and occupations evaluated were considered carcinogenic to humans, whilst 57 (7%) were considered as probably carcinogenic to humans (45).

The inclusion of an agent on the list of recognized human carcinogens usually indicates that adequate epidemiological data are available for evaluation and that sufficient evidence of a causal relationship exists. The emphasis on human data is problematic for several reasons. First, it demands human cancer cases prior to taking preventive action. Second, because most cancers have long latency periods before onset of disease, many additional cases will be diagnosed long after recognition of a problem and implementation of measures to restrict exposure. Third, when human exposure is erratic and occurs at levels that do not dramatically alter disease rates, or occurs primarily in conjunction with other exposures, the traditional morbidity and mortality studies will often not be large enough to detect risks. For example, increases in risk of $< 20\%$ are, in most instances, below the limits of what epidemiology can detect. Alternative approaches will be necessary to identify an agent as carcinogenic. It will always remain essential, however, that an evaluation of carcinogenicity is based on the available data in order to avoid the temptation of asking for missing data before taking public health action. To wait for epidemiological data when sufficient evidence for a cancer risk based on experimental results exists, can only result in avoiding or delaying the implementation of preventive measures.

Epidemiological criteria for establishing causality for chronic diseases, such as cancer, are stringent and demanding (44,48), although they were not originally intended to be interpreted rigidly. Whilst they have protected epidemiologists from falling into the trap of false positive results, they may also have allowed false negative findings and impeded the adoption of public health measures. It is also unfortunate that doubtful or negative epidemiological observations are inappropriately taken as more persuasive than positive results in rodent tests (49). In many instances results of traditional animal tests preceded and predicted similar effects in humans (e.g. 4-aminobiphenyl, DES, vinyl chloride, 1,3-butadiene, aflatoxin) (50–52).

Few single occupational cohorts are large enough to identify risks for all cancer sites. Furthermore few cohorts include women. Thus over-reliance on epidemiological findings gives the impression that other cancer sites (e.g. those common in women or those with a small number of expected tumors) are not related to occupational or environmental carcinogens. The strength of a study is, in addition, largely a feature of its sample size. Exposures that occur in small industries are thus not well covered by epidemiological research. Quality of exposure assessment and exposure misclassification can also affect the power of a study. The main target organs for the 70 agents evaluated by IARC as being carcinogenic to humans are, in descending order, lung (target of 23 complex exposures or chemicals), lymphopoietic system (13), urinary bladder (11), skin (7), liver (5), nasal sinuses (3), oral cavity (2), pharynx (2), larynx (2), esophagus (2), pleura (2), cervix (2), pancreas (1), breast (1), endometrium (1) and peritoneum (1). At first look it would therefore appear that some of the most common cancers, such as gastric cancer (the second most common tumor world-wide), colon–rectum, ovary, brain and prostate are not among these target organs, whilst breast, the most common tumor in women, is the target of only one known carcinogenic agent. However, if more attention were paid to epidemiological evidence that is suggestive but less than sufficient, then there would be clear indications that the digestive tract, brain, prostate and breast are also targets for a number of carcinogens.

The decreased acceptance of the capacity of experimental results (in particular of long-term rodent carcinogenicity tests) to predict similar effects in humans, has not completely undermined the use of these data to promote the adoption of precautionary measures. The IARC, for instance, has taken the official stand that ‘in the absence of adequate data on humans, it is biologically plausible and prudent to regard agents for which there is sufficient evidence of carcinogenicity

in experimental animals as if they presented a carcinogenic risk to humans' (53). OSHA regulates exposures in the workplace on the basis that agents for which there is sufficient experimental evidence of carcinogenicity are considered as human carcinogens. EPA adopted a similar policy, but the implementation of preventive measures concerning the general environment encounters considerable opposition from economic interests potentially affected by such regulation.

The list of human carcinogens and their target organs, might be quite different if: (i) epidemiological data were available for a larger proportion of human exposures for which there is experimental evidence of carcinogenicity; (ii) more attention were paid to epidemiological evidence that is suggestive of an exposure–cancer association, but is less than sufficient, particularly in identifying target organs; and (iii) experimental evidence of carcinogenicity supported by mechanistic considerations, were more fully accepted as predictions of human risk.

Effectiveness of reduction of exposures

Despite the clear expectation that primary intervention for occupational exposures should reduce cancer rates, this is not a research area that has received much attention. The time that must elapse after intervention before a reduction in cancer risk can be observed may be one explanation for the absence of such data. For many occupational carcinogens the latent period is up to 20 or more years. In the USA, where control of workplace carcinogens has primarily been implemented since the 1970s and 1980s, it is perhaps too early to observe a reduction in cancer rates. Data on smoking and lung cancer indicate that the relative risk of lung cancer among persons who stopped smoking did not begin to decline until 5 years after cessation and 50% reduction is not achieved until 15 or more years after stopping (6). The timing in the reduction in risk of lung cancer also appears to be related to the duration of smoking, i.e. the longer individuals have smoked the greater length of time after cessation is required before significant reduction in risks are observed. Men who had smoked for less than 20 years experienced a 60% reduction in relative risk 5–9 years after cessation. Individuals who smoked for 50 years or more experienced only a 7% decrease 5–9 years after cessation. The need for a lengthy period before reduced cancer risks can be observed for occupational exposures is also suggested by the evaluation of incidence and mortality rate for mesothelioma. Despite a significant reduction in high exposures to asbestos, rates for mesothelioma do not yet show significant declines. Most analyses predict that declines from intervention will not begin until well into the 21st century (54).

There are several methods, other than direct evaluation of cancer risks after reduction of exposure, that provide information of the effectiveness of exposure abatement, including: reductions in disease incidence when occupational exposures disappear; decreased risk among workers who leave an occupation; changes in risks with decreased exposure levels over time within a cohort; lower risks among those employed when exposures are lower; and decline in occupational cancer in routine statistics (e.g. scrotal cancer in England and Wales) (3). All three approaches support the effectiveness of exposure reduction in reducing disease risk. For example, trends in relative risks for nasal cancer point to the influence of effective exposure control. High rates of nasal cancer were associated with employment in the wood furniture industry in the early part of the 20th century. In a study from the Netherlands, individuals first employed after 1940 had considerably lower relative risks than those first entering the industry earlier (55). No case of nasal cancer was found among wood workers first exposed after 1941, when exposure to wood dust was reduced. This would not appear to be a short latency problem because the 40–50 years of follow-up seems more than adequate to observe an effect. Risk of lung cancer among chloromethyl ether workers has diminished among recently exposed individuals (56), where exposures are considerably lower. In this case, however, workers first employed in the late 1970s may not have had sufficient time to fully display the effect (3).

It is somewhat surprising, given the potential importance of the control of workplace exposures as a means to reduce cancer, that more direct data on the effectiveness of exposure intervention are not available. The lack of such studies may have several explanations. Public health policy tends to view the intervention as the final step in the disease reduction process. When this step is taken the evidence between exposure and disease is strong and prevention of disease is assumed from reduction of exposure. Research funding may be more difficult to obtain for studies to demonstrate the effectiveness of preventive actions than for investigations to identify etiology factors. Finally, not enough time may have elapsed for interventions on many recently identified occupational exposures to observe a reduction in cancer rates.

Primary prevention of smoking related diseases has been implemented at the individual level and at the societal level (e.g. regulations on smoking in public places), whereas responsibility for primary prevention of occupational or other environmental exposures may necessarily rest with industry. The tobacco industry has fought efforts to legislate primary prevention measures at every level. It is only through public pressure and personal responsibility that smoking prevention has been successful. In industry, however, individual workers are often powerless to take measures to prevent themselves from being exposed, except in the instance in which proper and consistent use of protective clothing and equipment is possible. Thus primary prevention must be implemented by society or by organizations that may have a vested interest in maintaining the status quo.

Dose–response and threshold

As most carcinogens exhibit a dose–response relationship, a simple corollary is that low exposures are likely to result in low excess risk and that lowering of exposure levels will result in a reduction of risk. Experimentally it has been demonstrated that lower doses of a chemical carcinogen result in a lower tumor incidence and in a delayed time of appearance of tumors (57). In the absence of a threshold, reduction even at the low end of the exposure range will have public health benefits that can be quite large where large segments of the population are affected. Recognized carcinogens with demonstrated dose–response relations are, among others, hexavalent chromium (58), radiation (59,60), benzidine (61,62), cadmium (63), tobacco smoke (4,6), asbestos (64,65), ethylene oxide (2) and benzene (66). For arsenic, dose–response curves are not linear, with a rise in risk that is sharper at lower than at higher exposures (67–70).

Thresholds appear plausible for acute toxicity effects and animal data are used to establish doses below which no acute adverse effects are expected to be observed (e.g. the No

Observable Adverse Effect Level or NOAEL). It is uncertain whether the threshold assumption can be justified for chronic effects, including cancer and non-cancer endpoints. Levels initially thought to provide safety are often proven to cause more subtle effects when agents are well studied. The case of lead is an example where, as more data accrue, the likelihood of threshold for neurological effects has become less plausible. For induction of cancer the standard assumption is that there is no threshold. Although this assumption has been challenged (16,71,72), its critics have not offered a clear method to identify any hypothesized threshold with reliability. In contrast, a theoretical understanding of the molecular basis of carcinogenesis would argue in favor of the non-threshold assumption, in particular by the fact that both solid tumors and leukemias carry, and possibly are the results of, multiple sequential alterations of the DNA of single cells and their progeny (73–75). These alterations may occur spontaneously or may be the result of the damaging action of a carcinogen. In addition, the rate of spontaneous mutations may be accelerated or increased by agents that induce cell proliferation (76). It appears prudent, as well as biologically plausible, to also extend the non-threshold assumption to non-genotoxic carcinogenic compounds (77,78).

The question of threshold is closely intertwined with the reversibility of damage and the related capacity of repair. The ability to repair DNA damage differs widely among individuals and may therefore be overwhelmed following different levels of exposure to a damaging agent. Furthermore, an individual's threshold is unlikely to remain constant and may fluctuate with stage of development, age, health status and other exposures.

Inherited genetic susceptibility may also affect possible threshold effects. This is clearest in the case of polymorphic carcinogen metabolism genes that are responsible for both activation and detoxification of carcinogens. Because of variable expression in different tissues and the variety of substrates acted upon, inheritance of a particular allele may place one at increased risk of one type of cancer or exposure, while decreasing the risk for a different type of cancer. Common inherited polymorphisms in other genes, e.g. those coding for DNA repair genes, receptors, and the normal homologues of oncogenes and tumor suppressor genes may also affect susceptibility to environmental exposure and thus affect risk in a variety of ways. As more susceptibility genes are identified, we may eventually be able to identify susceptible subpopulations and measure with some accuracy the varying risks associated with environmental exposure.

Regardless of the actual shape of the dose–response (linear, supra linear, sublinear), a non-threshold relation implies a positive health benefit from reduction of exposures. The public health benefit from reducing any exposure is a function of: (i) the number of persons exposed; (ii) the magnitude of the exposure changes; and (iii) the shape of the dose–response relationship. The steeper the dose–response curve, the greater the benefit for the same size population undergoing the same decrease in exposure.

Complex mixtures and low levels of exposures

Environmental exposures are usually studied individually, but we are actually exposed to a multitude of carcinogens, at once or in sequence. In a minority of cases only the causal association with a single agent can be reasonably claimed. Thus as risk is calculated for each single agent, the tacit assumption is made that there is no other carcinogen present and/or no synergistic effect on human cancer. This implies, however, that a level of exposure evaluated as 'safe' when based on single agents, may not be safe when the risk is calculated within the context of risks from exposures to other carcinogens (79,80).

The best known example of a complex carcinogenic mixture is tobacco smoke, which has been called 'the most deadly human carcinogen' (81). It is composed of a great variety of chemicals, many of which are carcinogenic and/or mutagenic (4) and occur in tobacco smoke at relatively low concentrations. Tobacco smoke provides the most convincing circumstantial evidence of an effective interaction between carcinogens, mutagens and possibly other modulating agents, at levels of exposure that, taken individually, may not represent a measurable hazard. Moreover, tobacco smoke probably does not cease to be carcinogenic when it is inhaled passively at concentrations that are considerably lower than those actively inhaled (82). By analogy it may be expected that there are other situations in which exposure to a variety of carcinogens/mutagens at low concentrations is responsible for an increase in cancer risk.

A case in point is exposure to atmospheric pollutants, which include several carcinogens at concentrations much lower than those at which their carcinogenicity was originally ascertained. They also include agents that do not act directly on DNA and would not traditionally be identified as chemical carcinogens, but were shown experimentally to increase the incidence of lung tumors through induction of chronic inflammation and a high concentration of free radicals (83). There is growing epidemiological evidence that even common levels of air pollution are associated with acute and chronic adverse effects on health, in particular on the respiratory tract, and include an increased risk of lung cancer (17,84–91). Public health action generally is not taken because of an alleged lack of biological plausibility based on the inability to confirm in the laboratory the epidemiological finding of long-term adverse effects of air pollution. As in other instances the small effect seen in the epidemiological studies has been interpreted as 'no evidence' and equated with no effect, with the clearly negative repercussions that such attitude has on public health, unavoidably delaying the adoption of preventive measures based on the reduction of exposure levels.

The time when it was particularly difficult to confirm experimentally the striking epidemiological evidence of the carcinogenicity of tobacco smoke has apparently been forgotten, as has the difficulty of confirming by experimental studies the epidemiological evidence of a risk for cancer from passive smoking.

Conclusions

Despite the enormous efforts and funds devoted to cancer research over several decades, improvements in cancer occurrence and survival, have, on the whole, been small. Cancer still remains a mainly lethal disease. Primary prevention remains the most relevant approach to reduce mortality through a reduction in incidence.

There is general agreement that environmental exposures are variously involved in the causation of the majority of cancer cases and that at least 50% of all cancers could be avoided by applying the existing etiologic knowledge. However, decisions on measures of primary prevention depend on many factors, including economic interests that may be given

an equal or sometimes greater weight than the scientific evidence for a potential health risk to humans.

The first requirement to declare an agent carcinogenic to humans presently is that epidemiological studies provide conclusive evidence of a causal relationship between exposure to the agent and human cancer. Identification of occupational and other environmental carcinogens is therefore generally based on a strong evidence of causal association that stems from the existence of human victims. On the other hand estimates of attributable risks that have been used to establish priorities in cancer research and control are instead often based on circumstantial or less than conclusive epidemiological evidence. The case of dietary factors is typical, to which 10 to 70% of all cancers have been attributed.

Experimental approaches to the identification of human carcinogens played an important role in the early experiments in the 1920s until the late 1960s, but thereafter their role has considerably diminished. The epidemiological approach first implied that epidemiological results were adequate to provide, by themselves alone, evidence of causal relationship. Later, the evidence provided by epidemiological data was often taken as the only acceptable proof of a causal association.

The inclusion of an agent or complex exposure in a list of recognized human carcinogens, therefore, usually indicates that adequate epidemiological data are available and they provide evidence of a causal relationship. It has been overlooked or forgotten that experimental results, in particular long-term carcinogenicity tests, have proven to be valid predictors of human risk. Too often epidemiological and experimental results are played against each other, whilst the most reasonable and scientifically correct approach is to evaluate the evidence of carcinogenicity on all data available.

The demonstration of a carcinogenic effect of chemicals submitted to a carcinogenicity test prior to their industrial production and introduction into the environment has certainly contributed to the primary prevention of human cancer, but it is impossible to express this in quantitative terms. There is an obvious logic in assuming that if exposure to an agent causes cancer, avoiding exposure to it prevents cancer. If the only acceptable evidence of carcinogenicity in humans depends on the existence of human victims, this invalidates principles of public health and primary prevention.

Effective primary prevention of cancer can be achieved by: (i) a reduction in the number of carcinogens to which humans are exposed; or (ii) a reduction in the exposure levels to carcinogens. The latter may be relevant even for exposure levels that are relatively low, for at least two reasons: (i) large sections of the population may be exposed to relatively low levels of exposure so that a further reduction may have a numerically important preventive effect; and (ii) exposure levels that could be seen as sufficiently low when based on single agents, may actually not be safe in the context of the many other concomitant risk factors.

Primary prevention has the double ethical privilege of intervening for the purpose of avoiding damage to health for the present and future generations, and of its universality, that is, its intrinsic characteristics of protecting all individuals without the potential for discrimination on socioeconomic grounds, which diagnostic and therapeutic approaches may unavoidably introduce.

Acknowledgements

The authors thank David Brown, Larry Fishbein, Peter Infante, Andrew Rowland and Ray Tennant for their interest and useful comments on the manuscript and Martha Taylor, Sandra Sandberg and Ashley Woods for their assistance in the preparation of the manuscript.

References

1. Schulte,P.A., Goldenhar,L.M. and Connally L.B. (1996) Intervention research: science, skills, and strategies. *Am. J. Ind. Med*., **29**, 285–288.
2. Stayner,L., Kuempel,E., Rice,F., Prince,M. and Althouse,R. (1996) Approaches for assessing the efficacy of occupational health and safety standards. *Am. J. Ind. Med.*, **29**, 353–357.
3. Swerdlow,A.J. (1990) Effectiveness of primary prevention of occupational exposures on cancer risk. In Hakama,M., Beral,V., Cullen,J.W. and Parkin,D.M. (eds), *Evaluating Effectiveness of Primary Prevention of cancer.* IARC Scientific Publication No. 103, Lyon, France, pp. 23–56.
4. IARC (1986) Tobacco smoke. In *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.* IARC Scientific Publication No. 38, Lyon, France.
5. Doll,R., Peto,R., Wheatley, K., Gray,R. and Sutherland,I. (1994) Mortality in relation to smoking: 40 years' observations on male British doctors. *Br. Med. J*., **309**, 901–911.
6. Lubin,J.H., Blot,W.J., Berrino,F., Flamant,R., Cillis,C.R., Kunze,M., Schmahl,D. and Visco,G. (1984) Modifying risk of developing cancer by changing habits in cigarette smoking. *Br. Med. J.*, **288**, 953–956.
7. Coleman,M.P., Esteve,J., Damiecki,P., Arslan,A. and Renard,H. (1993) *Trends in Cancer Incidence and Mortality.* IARC Scientific Publication No. 121, Lyon, France, pp. 1–806.
8. Bailar,J.C. and Smith,E.M. (1986) Progress against cancer? *N. Engl. J. Med.*, **314**, 1226–1232.
9. Cairns,J. (1985) The treatment of diseases and the war against cancer. *Sci. Am.*, **253**, 51–59.
10. Becker,N., Smith,E.M. and Wahrendorf,J. (1989) Time trends in cancer mortality in the Federal Republic of Germany: progress against cancer? *Intl J. Cancer*, **43**, 245–249.
11. Marshall,E. (1995) A new phase in the war on cancer. *Science*, **267**, 1412–1415.
12. Silbergeld,E. and Tonat,K. (1994) Investing in prevention: opportunities to prevent disease and reduce health care costs by identifying environmental and occupational causes of noncancer disease. *Toxicol. Ind. Health*, **10**, 675–810.
13. Smith,D.W.E. (1993) *Human Longevity.* Oxford University Press, Oxford and New York.
14. Coebergh,J.W.W. (1995) Summary and discussion of results. In Berrino,F. Sant,M. Verdecchia,A. Capocaccia,R. Hakulinen,T. and Esteve,J. (eds), *Survival of Cancer Patients in Europe*. IARC Scientific Publication No. 132, Lyon, France, pp. 447–463.
15. Davis,D.L., Dinse,G.E. and Hoel,D.G. (1994) Decreasing cardiovascular disease and increasing cancer among Whites in the United States from 1973 through 1987. Good news and bad news. *J. Am. Med. Assoc.*, **271**, 431–437.
16. Ames,N.N., Gold,L.S. and Willett,W.C. (1995) The causes and prevention of cancer. *Proc. Natl Acad. Sci. USA*, **92**, 5258–5265.
17. Forastiere,F., Corbo,G.M., Pistelli *et al*. (1994) Bronchial responsiveness in children living in areas with different air pollution levels. *Arch. Environ. Health*, **49**, 111–118.
18. Axelson,O., Davis,D.L., Forastiere,F., Schneiderman,M. and Wagoner,D. (1990) Lung cancer not attributable to smoking. *Ann. N.Y. Acad. Sci.*, **609**, 165–178.
19. Geddes,M., Balzi,D. and Tomatis,L. (1994) Progress in the fight against cancer in EC countries: Changes in mortality rates, 1970–1990. *Eur. J. Cancer Prev.*, **3**, 31–44.
20. L.A.Gloeckler Ries *et al*. (eds) (1994) *SEER Cancer Statistics Review.* NCI, NIH Publication No. 94–2789, Bethesda, MD.
21. Polednak,A.P. (1994) Projected numbers of cancers diagnosed in the US elderly population, 1990 trough 2030. *Am. J. Public Health*, **84**, 1313–1316.
22. Devesa,S.S., Blot,W.J., Stone,B.J., Miller,B.A., Tarone,R.E. and Fraumeni,J.F.Jr (1995) Recent cancer trends in the United States. *J. Natl Cancer Inst.*, **87**, 175–182.
23. Blair,V. and Birch,J.M. (1994) Patterns and temporal trends in the incidence of malignant disease in children: I. Leukaemia and lymphoma. *Eur. J. Cancer*, **30A**, 1490–1498.
24. Blair,V. and Birch,J.M. (1994) Patterns and temporal trends in the incidence of malignant disease in children: II. Solid tumours of childhood. *Eur. J. Cancer*, **30A**, 1498–1511.
25. Desch,M.D. and Bleyer,W.A. (1994) Amended long-term trends in cancer incidence rats in children. *J. Natl Cancer Inst.*, **86**, 1481–1482.
26. Edwards,B.K. and Hankey,B.F. (1994) Response. *J. Natl Cancer Inst.*, **86**, 1482.

27. Wynder,E.I. and Gori,G.B. (1977) Contribution of the environment to cancer incidence: An epidemiological exercise. *J. Natl Cancer Inst.*, **58**, 825–832.
28. Higginson,J. and Muir,C.S. (1979) Environmental carcinogenesis: Misconceptions and limitations to cancer control. *J. Natl Cancer Inst.*, **63**, 365–384.
29. Doll,R. and Peto,R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J. Natl Cancer Inst.*, **66**, 1191–1308.
30. Tomatis,L., Aitio,A., Day,N.E., Heseltine,E., Kaldor,J., Miller,A., Parkin,D.M. and Riboli,E. (eds) (1990) *Cancer: Causes, Occurrence and Control.* IARC Scientific Publication No. 100, Lyon, France.
31. Tominaga,S. (1994) Risk factors of importance in the 21st century—Can they be controlled? In *Proceedings of the XVI International Cancer Congress*, UICC, p. 313.
32. Zahm,S.H., Fraumeni,J.F.Jr and Davis,D.L. (eds) (1995) The avoidable causes of cancer. *Environ. Health Perspect.*, **103**, 129–320.
33. Doll,R. (1996) Nature and nurture: possibilities for cancer control. *Carcinogenesis*, **17**, 177–184.
34. Huff,J.E., Haseman,J.K. and Rall,D.P. (1991) Scientific concepts, value, and significance of chemical carcinogenesis studies. *Ann. Rev. Pharmacol. Toxicol.*, **31**, 621–652.
35. Magnani,C., Terracini,B., Ivaldi,C., Botta,M., Mancini,A. and Andrion,A. (1995) Pleural malignant mesothelioma and non-occupational exposure to asbestos in Casale Monferrato, Italy. *Occup. Environ. Med.*, **52**, 362–367.
36. Henderson,B.E., Ross,R.K. and Pike,M.C. (1991) Toward the primary prevention of cancer. *Science*, **254**, 1131–1138.
37. Anonymous (1996) Is health a moral responsibility? *Lancet*, **347**, 1197.
38. World Health Organization (1964) *Prevention of Cancer*, World Health Organization Technical Report Series No. 276, Geneva, Switzerland.
39. Tsutsui,H. (1918) Ueber das kunstlich erzeugte Cancroid bei der. Maus. *Gann*, **12**, 17–21.
40. Passey,R.D. (1992) Experimental soot cancer. *Br. Med. J.*, **ii**, 1112–1113.
41. Pott,P. (1765) *Chirurgical Observations Relative to the Cataracts, the Polypus of the Nose, the Cancer of the Scrotum, the Different Kinds of Ruptures and the Mortifications of the Toes and Feet.* Hawes, Clarke and Collins, London.
42. Berenblum,I. and Shubik,P. (1947) The role of croton oil applications, associated with a single painting of a carcinogen, in tumour induction of the mouse's skin. *Br. J. Cancer*, **1**, 379–382.
43. Foulds,L. (1969) *Neoplastic Development*. Academic Press, London.
44. Bradford Hill,A. (1971) *Principles of Medical Statistics*. The Lancet Ltd, London.
45. IARC (1972–1996). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vols 1–66. IARC Scientific Publications, Lyon, France.
46. Ember,L. (1984) Study confirms paucity of chemical toxicity data. *Chem. Eng. News*, **62**, 12.
47. Fung,V.A., Barrett,J.C. and Huff,J. (1995) The carcinogenesis bioassay in perspective: application in identifying human cancer hazards. *Environ. Health Perspect.*, **103**, 680–683.
48. Rothman,K.J. (1986) *Modern Epidemiology.* Little, Brown and Co., Boston.
49. Higginson,J. (1985) DDT: Epidemiological evidence. In Wald,N.J. and Doll,R. (eds), *Interpretation of Negative Epidemiological Evidence for Carcinogenicity.* IARC Scientific Publication No. 65, Lyon, France, pp. 107–117.
50. Tomatis,L. (1979) The predictive value of rodent carcinogenicity tests in the evaluation of human risks. *Ann. Rev. Pharmacol. Toxicol.*, **19**, 511–530.
51. Huff,J. (1993) Chemicals and cancer in humans: First evidence in experimental animals. *Environ. Health Perspect.*, **100**, 201–210.
52. Vainio,H., Wilbourn,G. and Tomatis,L. (1996) Identification of environmental carcinogens: The first step in risk assessment. *Adv. Modern Environ. Toxicol.*, **xxiii**, 1–19.
53. IARC (1987) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7. IARC Scientific Publications, Lyon, France.
54. Peto,J., Hodgson,J.T., Matthews,F.E. and Jones,J.R. (1994) Continuing increase in mesothelioma mortality in Britain. *Lancet*, **345**, 535–539.
55. Hayes,R.B., Gerin,M., Raatgever,J.W., de Bruyin,A., Woof- (1986) Related exposure and sinonasal cancer. *Am. J. Epidemiol.*, **124**, 569–577.
56. Maher,K.V. and DeFonso,L.R. (1987) Respiratory cancer among chloromethyl ether workers. *J. Natl Cancer Inst.*, **78**, 839–843.
57. Littlefield,N.A., Farmer,J.H., Gaylor,D.W. and Sheldon,W.G. (1979) Effects of dose and time in a long-term, low dose carcinogenic study. *J. Environ. Path. Toxicol.*, **3,** 17–34.
58. Mancuso,T.F. (1975) Considerations on chromium as an industrial carcinogen. *International Conference on Heavy Metals in the Environment*. Toronto, Canada , 27–31 Oct, pp. 343–356.
59. National Research Council (1991). *Health Effects of Exposure to Low Levels of Ionizing Radiation* (Committee on the Biological Effects of Ionizing Radiation V). National Academy Press, Washington, DC.
60. Wing,S., Shay,C.M., Wood,J.L., Wolf,F., Craigle,D.L. and Frome,E.L. (1991) Mortality among workers at Oak Ridge National Laboratory: Evidence of radiation effect. *J. Am. Med. Assoc.*, **265**, 1397–1402.
61. Case,R.A.M., Hosker,M.E., McDonald,D.B. and Pearson,J.T. (1954) Tumours of the urinary bladder in workmen engaged in the manufacture and use of certain dyestuff intermediates in the British chemical industry. Part I. The role of aniline, benzidine, alpha-naphthylamine and beta-naphthylamine. *Br. J. Ind. Med.*, **11**, 75–104.
62. Zavon,M.R., Hoegg,U. and Bingham,E. (1973) Benzidene exposure as a cause of bladder tumors. *Arch. Environ. Health*, **27**, 1–7.
63. Stayner,L., Smith,R., Thun,M., Schnorr,T. and Lemen,R. (1992) A dose–response analysis and quantitative assessment of lung cancer risk and occupational cadmium exposure. *Ann. Epidemiol.*, **2**, 177–194.
64. Selikoff,I.J., Hammond,E.C. and Siedman,H. (1979) Mortality experience of insulation workers in the United States and Canada. *Ann. N.Y. Acad. Sci.*, **330**, 91–116.
65. Dement,J.M., Brown,D.P. and Okuna,A. (1994) Follow-up study of crysotile asbestos textile workers: cohort mortality and case-control analyses. *Am. J. Ind. Med.*, **26**, 431–447.
66. Rinsky,R.A., Young,R.J. and Smith,A.B. (1981) Leukemia in benzene workers. *Am. J. Ind. Med.*, **2**, 217–245.
67. Lee-Feldstein,A. (1986) Cumulative exposure to arsenic and its relationship to respiratory cancer among copper smelter employees. *J. Occup. Med.*, **28**, 296–303.
68. Enterline,P.E., Henderson,V.L. and Marsh,G.M. (1987) Exposure to arsenic and respiratory cancer: A reanalysis. *Am. J. Epidemiol.*, **125**, 929–938.
69. Jarup,L., Pershagen,G. and Wall,S. (1989) Cumulative arsenic exposure and lung cancer in smelter workers: A dose–response study. *Am. J. Ind. Med.*, **15**, 31–41.
70. Hertz-Picciotto,I. and Smith,A.H. (1993) Observations on the dose–response curve for arsenic and lung cancer. *Scand. J. Work Environ. Health*, **19**, 217–226.
71. Purchase,I.F.H. and Auton,T.R. (1995) Thresholds in chemical carcinogenesis. *Reg. Toxicol. Pharmacol.*, **22**, 199–205.
72. Williams,G.M., Karbe,E., Fenner-Crisp,P., Iatropoulos,M.J. and Weisburger,J.H. (1996) Risk assessment of carcinogens in food with special consideration of non-genotoxic carcinogens. *Exp. Toxic Pathol.*, **48**, 209–215.
73. Nowell, P.C. (1991) How many human cancer genes? *J. Natl Cancer Inst.*, **83**, 1061–1064.
74. Weinberg,R.A. (1991) Tumor suppressor genes. *Science*, **254**, 1138–1146.
75. Shields,P.G. and Harris,C.C. (1991) Molecular epidemiology and the genetics of environmental cancer. *J. Am. Med. Assoc.*, **266**, 681–687.
76. Melnick,R.L. and Huff,J.E. (eds) (1993) Cell proliferation and chemical carcinogenesis. *Proc. Environ. Health Perspect.*, **101** (Suppl. 5), 1–285.
77. Hoel,D.G. and Portier,C.J. (1994) Nonlinearity of dose–response functions for carcinogenicity. *Environ. Health Perspect.*, **102**, 109–113.
78. Melnick,R.L., Kohn,M.C. and Portier,C.J. (1996) Implications for risk assessment of suggested nongenotoxic mechanisms of chemical carcinogenesis. *Environ. Health Perspect.*, **104**, 123–133.
79. Schmahl,D., Preussman,R. and Berger,D.R. (1989) Causes of cancer—An alternative view to Doll and Peto (1981). *Klin. Wochenschr.*, **67**, 1169–1173.
80. Sugimura,T. (1992) Multistep carcinogenesis: A 1992 perspective. *Science*, **258**, 603–607.
81. Peto,R. (1994) Smoking and death: The past 40 years and the next 40. *Br. Med. J.*, **309**, 937–939.
82. National Institutes of Health (1993) *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders*, Monograph No. 4; NIH Publication No. 93-3605, Bethesda, MD.
83. Harris,C.C. (1995) *p53*: At the crossroads of molecular carcinogenesis and risk assessment. *CIIT Activities*, **15**, 1–6.
84. Pershagen,G. and Simonato,L. (1990) Epidemiological evidence on air pollution and cancer. In Tomatis, L. (ed.), *Air Pollution and Human Cancer.* Springer–Verlag, Berlin, pp. 63–74.
85. Dockery,W, Pope,A.C., Xu,X., Spengler,J.D., Ware,J.H., Fay,M.E., Ferris,B.G.Jr and Speizer,F.E. (1993) An association between air pollution and mortality in six US cities. *N. Engl. J. Med.*, **329**, 1753–1759.
86. Schwartz,J. (1994) Air pollution and daily mortality: a review and meta analysis. *Environ. Res.*, **64**, 36–52.
87. Dockery,W. and Pope,A.C. (1994) Acute respiratory effect of air pollution. *Ann. Rev. Pub. Health*, **15**, 107–132.
88. Xu,X., Li,B. and Huang,H. (1995) Air pollution and unscheduled hospital outpatient and emergency room visits. *Environ. Health Perspect.*, **103**, 286–289.

89. Barbone,F., Bovenzi,M., Cavallieri,F. and Stanta,G. (1995) Air pollution and lung cancer in Trieste, Italy. *Am. J. Epidemiol.*, **141**, 1161–1169.
90. Pope,C.A.III, Thun,M.J., Namboodiri,R.N., Dockery,D.W., Evans,J.S., Speizer,F.E. and Heath,C.W.Jr (1995) Particulate air pollution as a predictor of mortality in a prospective study of US adults. *Am. J. Respir. Crit. Care Med*., **150**, 669–674.
91. Anderson,N.R., Ponce de Leon,A., Bland,J.M., Bower,J.S. and Strachan,D.R. (1996) Air pollution and daily mortality in London: 1987–1992. *Biol. Med. J*., **312**, 665–669.

Received on June 23, 1996; revised on August 8, 1996; accepted on August 14, 1996.