Identification of Carcinogenic Agents and Primary Prevention of Cancer

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ABSTRACT: ***During the annual Ramazzini Days, the Mayor of Carpi confers the Ramazzini Award on scientists deemed by the Collegium Ramazzini to have made outstanding contributions to furthering the aims of Bernardino Ramazzini in safeguarding public health. Dr. Lorenzo Tomatis was the Ramazzini Award recipient in 2005, and the presentation of the award was a highlight of the Symposium. The Ramazzini Lecture given by Dr. Tomatis follows.***

INTRODUCTION

In his introduction to *De morbis artificum diatriba*, Bernardino Ramazzini states modestly that his book was not inspired by a desire for glory but by a sense of duty; he had no pretensions to write a great work of art but wrote it for the good of the community and workers. Ramazzini exemplifies how science, legal justice, and social equity can harmoniously and efficiently coexist in a competent, sensible, committed physician. In our society, these three qualities rarely converge. Social equity is the most consistently maltreated of the three, while science is generally considered, by definition, to be above criticism while deliberately ignoring the possibility that its objectivity is often blurred by conflicts of interests.

One of the main merits of Bernardino Ramazzini is that he made physicians aware of questions other than those raised traditionally, that is about the nature of the work one is doing (quam artem exerceat), and of an area of medical concern that Hippocrates had neglected and scientific medicine did not consider part of its duties, which is the health of workers.[1] Even though Ramazzini's descriptions of working conditions and recommendations for their improvement necessarily refer to the preindustrial period, they are still largely valid today as is his emphasis on primary prevention.

Prevention, and specifically primary prevention, is the subject of my presentation. It might appear unnecessary to recall the distinction between primary and secondary prevention, but a look at the current scientific literature indicates some sort of oblivion, such that secondary prevention appears to be considered

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the only means of prevention and chemoprevention in an ill-defined territory between the two. Considerable advances in our understanding of the mechanisms of progression of early cancerous lesions have moved the emphasis from a combined etiopathogenetic approach to the study of disease to a merely pathogenetic one. For instance, the program of an International Conference on Frontiers in Cancer Prevention to be held in October of 2005 and advertised as the "world's most comprehensive, transdisciplinary cancer prevention meeting," shows an excellent scientific level devoted mainly to early diagnosis, screening, genetic predisposition, and chemoprevention, while research on the etiology of cancer, directly related to primary prevention, represents only a minor part of the program. The sort of aristocratic tendency that between the time of Hippocrates and that of Bernardino Ramazzini led to dismissal of the occupational diseases of the working class by scientific medicine, or at least by a large sector of the biomedical establishment, is continuing today with the priority given to intellectually stimulating research, which usually has potential economic outcomes as its implicit but rarely declared goal. In this context, the pharmaceutical industry plays both a direct and an indirect role by the conditioning effect of its conspicuous financial support.

DIFFICULTIES OF PRIMARY PREVENTION OF CANCER

For a long time, research on primary prevention and the promotion of sanitary and social equity was hindered not only by a relative scarcity of funds but also by the difficulty, if not the impossibility, of obtaining financial support for certain projects. Today, financial support to several areas of research is more abundant; thus, the excuse that certain projects cannot be supported because of lack of funds might be questioned. A different, indirect but efficient system has been used for some time to block research that is considered not to be in the interests of the dominant economic power and consists of generously financing preselected areas of research, thus attracting scientists to objectives other than the protection of public health. The major flow of funds is toward large clinical trials and investigations on mechanisms of action or genetic predisposition, the results of which are widely advertised and guarantee access to important scientific journals. Some of the projects are useful and innovative, while others can be implemented only with a huge economic and organizational effort made possible by the availability of funds. This not to say that such research should not be done but that it should not stifle research projects that are uncongenial to the economic power.

Blockage by lack of funds has thus been replaced by blockage via a plethora of funds. To resist the attraction of abundant, secure funding, the publication of results in journals with high impact factors, and an opening to a brilliant career, much courage, determination, and a spirit of sacrifice are needed as they were needed years ago to start and persist in research on prevention with scarce or inadequate funding. That there are still scientists who have such courage

and determination is one of the few reassuring signs in the present greedy, ruthless era.

Primary prevention, with the aim of preventing the occurrence of disease, and with indiscriminate universality as one of its main characteristics, should always have high priority. The primary prevention of infectious diseases did not encounter serious resistance, except for the reluctance of certain groups to accept systematic immunization, and was therefore solidly built on international cooperation. If primary prevention of infectious diseases has not been implemented with the same care and efficiency throughout the world, it is not because of doubts about the etiological agents of the diseases, which, once identified, nobody denied their being equally pathogenic at all latitudes, but because of the perverse combination of extreme poverty in certain countries, the irreducible selfishness of the rich countries, and the greed of multinational corporations.

Primary prevention of cancer of occupational and environmental origin, instead, has often stumbled on an obstacle course, and the identification of a chemical or physical agent as carcinogenic has too often met with skepticism, if not open hostility. Some chemical compounds were recognized as carcinogens in some countries and not in others, and even where they have been recognized as carcinogenic, the permitted or accepted concentrations varied considerably from country to country, as if their carcinogenicity could disappear or change at certain borders.[2,3]

The very long delay between the identification of a carcinogenic agent and adoption of adequate measures of prevention cannot be explained by a lack of advanced, specific medical procedures, as was the case in the early fight against some infectious diseases. The measures taken have generally been late and incomplete, coming only after the damage had spread and even then rarely providing total protection. The prevailing assumption, also used as an improper justification, was that the production of certain goods is necessary and vital, even when it was only aimed at increasing consumption of inessential goods, and that the risks involved in their production are an unavoidable price that society must pay. This attitude steadily disregarded the evidence that the highest price is paid by a particular sector of the population, in which morbidity and mortality are considerably higher than those in the rest of the population.

Ionizing radiation is a good example of how the appearance of evidence of the carcinogenicity of an environmental agent is not necessarily followed by adoption of measures of prevention and often not by even elementary prudence. Seven years after the discovery of X rays by Roentgen in 1895,[4] two reports were published describing their induction of malignant tumors of the skin[5,6]; this was an exceptionally short lag between the introduction of an agent into the environment and demonstration of its dangers. Neither radiologists nor health authorities nor the public, however, appeared to pay much attention to the possible risks associated with the use of X rays. Given their immense usefulness for diagnostic and therapeutic purposes, it was perhaps luckily so; nevertheless, we must also regret that their use increased in an almost total

absence of caution. The case of ionizing radiation also shows the difficulties that are met in gaining acceptance of the dangers of small doses, both at work and in the general environment. It took 40 more years before the carcinogenicity of natural radiation was recognized when it was finally acknowledged as the cause of tumors in Schneeberg miners.[7] It took several more decades before it was officially accepted that the general population was at risk from exposure to natural radiation at levels much lower than those found in the environment of the mines.[8] An excess risk for cancer was recently shown[9] at doses and dose rates of radiation that for decades have been proclaimed as safe, in a climate of recent evidence that exposure to background radiation has slightly increased over the past few years.[10] As for other environmental agents, economic and political interests have interfered substantially with priorities in the defense of public health.

On the occupational front, benzene, for which evidence of carcinogenicity goes back to the 1920s, is one of the most important examples. The concentration of 100 ppm officially accepted in 1946 was sharply reduced to 10 ppm in 1978, even though the knowledge about its carcinogenicity was substantially the same at those two dates. Nor was existing knowledge much more advanced in the 1990s, when the maximum acceptable concentration was lowered to 1 ppm and a concentration of 0.3 ppm was proposed. The evolution of acceptable concentrations was not driven by progress in understanding of the mechanisms underlying the carcinogenicity of benzene or by an increased attention to occupational risks by the industries concerned or the health authorities, but was instead the result of the struggle for health by workers, unions, and concerned physicians and scientists against formidable economic interests.[11] In spite of the fact that the hemotoxicity of concentrations less than 1 ppm was recently further confirmed,[12] powerful industrial interests are still trying to undermine recognition of the risk of low concentrations.

Asbestos is probably the most dramatic[13,14] of the examples that provide evidence of a discrepancy between scientific evidence of an adverse effect and its translation into adequate preventive measures. Because of the determination of powerful economic interests to maintain the level of their profits at all costs, no international agreement yet exists to ban the production and use of asbestos worldwide, and more than 2 million tons are still produced annually. While progress is slowly being made in the right direction, some rich countries continue to exploit the permissive or absent occupational legislation in poor countries and send them old ships, stuffed with asbestos, to be demolished.[15]

BIRTH OF INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC)

Implementation of primary prevention is associated, to a considerable degree, with attribution of risks. This clearly depends on the availability of data on a number of risk factors so that plans for intervention can be for-

mulated on the basis of urgency, feasibility, and priorities, depending on the relevance of the risks. The best known and most reliable sources of information on human carcinogens are those based on evaluations made by IARC[16] and the National Toxicology Program (NTP).[17] As the IARC started its program of evaluations several years earlier than the NTP, it has data on many more agents.

Retrospectively, the period when the IARC was created can be looked upon as a time of widespread enthusiasm and hope in cancer research. It was also a time when the idea that primary prevention had to be a high priority in the fight against cancer seems to have reached some of the greatest world authorities and when the stated intentions of politicians were implemented with an astonishing rapidity, rarely if ever seen in international affairs. On November 8, 1963, 12 eminent French personalities from widely differing backgrounds, including the oncologist Antoine Lacassagne, the biologist Jean Rostand, the writer Francois Mauriac, and the architect Charles Le Corbusier, approached the President of France, Charles de Gaulle, and invited him to take up a universal strategy of research to fight one of the greatest threats to human kind: cancer. The emotion that President de Gaulle had recently experienced in visiting two persons to whom he was particularly attached, both dying of cancer, may have played a role in the swiftness of his favorable response. General de Gaulle asked the ministers of foreign affairs of wealthy countries that had contributed substantially to cancer research and control worldwide (besides France, the United Kingdom, the United States, and the USSR) and the Director General of the World Health Organization (WHO) to meet in Paris to discuss how to implement a common initiative. The foreign ministers of two additional countries, namely the Federal Republic of Germany and Italy, were later also asked to attend the meeting that took place in December 1963.[18]

Thanks to the strength of its basic ideals, the initiative generously and vigorously proposed by France managed to survive, in spite of some hostility from the International Union against Cancer (the oldest and at the time the most important international organization for cancer control, better known under the French abbreviation UICC), which, while adhering in theory to an increased boost to cancer research, did not hide its lack of enthusiasm about the creation of an institution that would escape its control. There was also some resistance from the heads of national cancer centers, who supported the initiative in principle but feared that a new international organization would divert funds and competent scientists from their own institutes.[18] The initiative kept its original public health orientation, but it was not equally successful in stimulating the financial generosity of the states.

IDEALISM AND REALISM OF FUNDING

The original proposal of General de Gaulle was that the new international institution be endowed with 0.5% of the military expenditure of the participating

states. On the basis of estimates of the 1965 defense budgets of the first six states that adhered to the French initiative, 0.5% would have meant about US$ 400 million annually (0.5% of the estimated defense budget of the United States alone would have been about US$265 million). Funding of the new institution at the level originally proposed would have meant a considerable boost for cancer research. The first six member states finally agreed on a much more modest annual contribution of US$150,000 each, so that the initial annual budget of IARC was US$900,000—400 times less than it would have been if the original French proposal had been accepted. The budget did increase over the years as more states joined the agency, and a statutory budget of US$37 million was granted to the agency by its governing council for the biennium 2004–2005; 0.5% of the estimated amount spent for "defense" by the 16 states presently participating to the agency in just 1 of those 2 years would have represented about US$2 billion.

In accordance with the statutes approved by the World Health Assembly on May 20, 1965 in Geneva and with advice given by the governing and scientific councils, it was agreed that the agency, in line with its international role, should establish a program of permanent activities that included: (*a*) collection and dissemination of information on the epidemiology of cancer and cancer research in both developed and developing countries; (*b*) identification of the causes of cancer; and (*c*) promotion of international collaboration in cancer prevention worldwide.[19,20] Lyon, France was chosen as the site for IARC, which officially started its activities in May 1967.

The coexistence under the same roof of offices and laboratories, together with an efficient administration, favored multidisciplinarity, which was a strong characteristic of several IARC programs from the beginning. The fact that the agency could offer laboratory facilities actively involved in planning and conducting research made it possible to attract competent scientists from various backgrounds, including pathologists, biochemists, chemists, toxicologists, and virologists, as well as epidemiologists and biostatisticians. In this way, IARC was able to build up scientific teams that could interact and collaborate efficiently on an equal basis with scientists in any other research institute in the world.

IARC MONOGRAPH PROGRAM

Among the first activities of the agency were the collection and processing of data on morbidity and mortality from cancer, an educational program and evaluation of carcinogenic risks to humans. For the purpose of this presentation, I shall focus on the last of these basic activities, although the other two and several other projects were very successful and deserve full recognition. When, in 1968, the agency was requested to provide a list of human carcinogens, two reliable, albeit incomplete lists of human carcinogens were available: one

proposed by Hueper and Conway[21] comprising 17 agents or groups of agents considered definitely carcinogenic to humans and one by WHO that consisted of 16 agents.[22]

The IARC Monograph Program was initiated in 1969; in 1972, the first volume of the *IARC Monographs* was published in a series that became known worldwide as the "orange books." To date, 85 volumes of *Monographs* have been published and four additional volumes are in press, covering 900 agents (chemicals, groups of chemicals, complex mixtures, occupational exposures, biological agents, cultural habits, physical agents).

Individual agents and complex exposures are assigned to different groups, according to the level of evidence for their carcinogenicity: group 1, human carcinogens, presently consists of 95 entries; group 2A, probable human carcinogens, has 65 entries; group 2B, possible human carcinogens, has 240; group 3, not classifiable for carcinogenicity in humans, has 608; and group 4, probably not carcinogenic to humans, has 1. Leaving out for the moment group 3, but keeping in mind that the limitation and inadequacy of the evidence of carcinogenicity for the agents included in this group may not be necessarily related only to the characteristic of their biological interactions but also to the quality and quantity of available data, there are 403 agents for which there is evidence of a causal association with cancer in humans with decreasing strength from group 1 to group 2B.

To my knowledge, in spite of a number of attempts, no one has yet succeeded in dislodging an agent from IARC group 1 and dragging it toward incertitude. Nevertheless, although it has been impossible to deny the evidence for agents in group 1, the carcinogenicity of certain compounds has been limited to the induction of particular tumor types, with doubt cast on or a denial of causal associations with other types of tumors. For instance, while no one dares to deny that vinylchloride causes liver angiosarcoma, a conspicuously vocal fraction of the scientific establishment maintains that there is no causal association between vinylchloride and liver tumors of other histological types or with tumors in other organs.

Another example is formaldehyde, reevaluated by IARC in 2004[23] and transferred to group 1 from group 2A, to which was assigned in 1987 and again in 1995. *A posteriori*, one might wonder whether the hesitancy manifested in 1987 and in 1995 was justified, but at least in 2004 it was finally recognized as a human carcinogen. The acceptance of evidence for its carcinogenicity is, however, limited to the induction of rhino pharyngeal carcinoma, while the evidence for an association with myeloid leukemia is reported to be strong but not sufficient, and only limited evidence is available for an association with sino nasal cancer. One may ask whether the hesitation present even in this much more advanced last evaluation serves public health well. There is, for instance, a real possibility of domestic exposure to formaldehyde indoors, which mainly concerns children. It is not easy to establish the extent to which exposure to low concentrations of a carcinogen represents a risk for the rest of one's life

when the exposure occurs at an age of particular fragility in certain aspects and which, by definition, allows the longest possible time for a long-term effect to manifest. The difficulty of designing an adequate epidemiological study on such effects is an expression of the limitations of our methods of investigation. Nevertheless, awareness of these limitations should encourage a greater commitment to primary prevention instead of leading toward an *a priori* denial or even ignoring the possibility of a long-term risk.

The Predominant Role of Epidemiology

It is interesting that the inception of the *IARC Monographs* program in the late 1960s coincided with the rise of epidemiology as the fundamental discipline in the assessment of risk for noncommunicable diseases, including cancer. This was a considerable change from the attitude that had prevailed since 1922, when Passey[24] succeeded in inducing malignant skin tumors in mice with soot extracts; his results were taken as definitive confirmation of the observations of Percival Pott, implying that clinical and epidemiological observations had to be confirmed experimentally in order to be accepted. After it was agreed in the early 1970s that epidemiological results could by themselves prove causation, the view that only the epidemiological approach could provide acceptable evidence for a causal relationship between an exposure and human cancer began to prevail. A first consequence was that experimental results, in particular those of long-term bioassays, were considered of secondary importance. A second consequence was that epidemiologists began to attempt quantification of risks attributable to certain causes and to calculate, admittedly roughly, the proportions of cases that could be avoided by efficient prevention. The best-known attempts were those of Wynder and Gori[25] and Higginson and Muir[26] and, most elaborately and in greatest detail, by Doll and Peto.[27] All three studies attributed the great majority of tumors to environmental causes and agreed that the most relevant risk factors were related to lifestyle, in particular tobacco use and dietary habits, which were reported to be responsible for 60–70% of cancers, with greatly lower estimates for those due to occupational and other environmental exposures.

Tobacco undeniably plays an essential role in increasing the human cancer burden, and there is little doubt that a better social and health-oriented education could help individuals in being more conscious and responsible in the choice of their life habits. However, the emphasis given to lifestyle factors, to the detriment of information on the role of chemical pollutants, favored the uninterrupted production of agents with negative effects on health that remain hidden or secret or are deliberately underestimated. Furthermore, attributing most cancer cases to lifestyle, which is interpreted as being related to free personal choice, unduly amplifies the individual's responsibility, diverts attention from the lack of commitment of health authorities, and obscures the etiological role of other risk factors.[28]

An Incoherent Attribution of Risks

The way in which attributable risks are considered is incoherent, as unequal degrees of evidence for the carcinogenicity of various factors are treated equally.[28] A necessary requirement for declaring an environmental chemical carcinogenic to humans is that conclusive epidemiological studies support a causal relationship, and particularly robust evidence for an association between an occupational exposure and human cancer is required before a causal association is accepted. The evidence for a contribution of dietary factors to the cancer burden is usually circumstantial and, in some instances, rather weak. Punctilious precision is used in calculating occupational and environmental risks, while wide latitude is allowed for risks related to diet, ranging between 10% and 70%. It was recognized, however, that the occupational carcinogens identified so far "tend to be those which increase the risk of some particular type(s) of cancer very substantially," and that other occupational carcinogens might not have been detected simply because they have not been investigated or because the exposure concerns a small number of individuals, and no suspicion was raised.[27]

AN ELEGANT AMBIGUITY

On the one hand, it was recognized that certain industrial products present in the general environment (for instance, pesticides) can increase the frequency of tumors; on the other hand, their identification as risk factors was made to depend on finding that they are carcinogenic in situations in which the exposure is very high, such as during occupational exposure. Such findings, however, depend in turn on an obligatory series of circumstances, such as a preexisting suspicion of carcinogenicity, a sufficient number of exposed individuals to ensure the statistical validity of the observations, and a sufficiently long duration of exposure and of follow-up. Magnifying the difficulties in providing convincing evidence of an increased cancer risk with endless discussions on the statistical credibility of the data, may have also contributed to focus the attention mainly, if not exclusively, on cancer, and in this way divert the attention from other adverse health effects. It was further recognized that some substances but, as carefully specified, certainly not all, for which there is experimental evidence of carcinogenicity, even if obtained at doses much higher than those to which humans are generally exposed, could have the same effect in humans.

This way of presenting and interpreting data casts light on a particularly elegant ambiguity that has allowed a coupling of certainty about risks proclaimed as ascertained and convincing with wide areas of shadow. These shadowy areas, to which consistent components of the etiology of cancer were relegated, have attracted insufficient attention, largely because research on mechanisms, often related to new therapeutic approaches and to the genetic component of

risk, has greatly expanded to the detriment of studies on etiology and primary prevention, the latter being focused almost exclusively on the role of lifestyle.[29]

The assignment of a compound to one of the groups proposed by IARC can have important consequences for the determination of attributable risks and translation into measures for primary prevention. Most agents assigned to group 1 and several of those assigned to group 2A are dealt with as human carcinogens and are subjected to strict legislation. Group 2B, however, represents a large parking lot in which 240 agents have been stored because of the relative inadequacy of the experimental and epidemiological evidence of carcinogenicity. The systematic undermining of the significance of long-term carcinogenicity tests and the extreme caution with which some epidemiologists assess evidence for risk for fear of being accused of creating false-positive results emphasize these inadequacies. The relative inadequacy or the absence of epidemiological data, however, cannot be considered equivalent to negative findings, nor can it be considered more relevant for public health than positive experimental findings.

The probability that additional epidemiological data will become available in the near future on compounds assigned to group 2B, to avoid indefinite extension of their storage in this parking lot, is rather remote. Given the objective difficulties of designing adequate studies capable of credibly demonstrating risks of low or medium level and the access of the results of such studies only to journals with low impact factors, agents assigned to group 2B have not raised the interests of epidemiologists. Similarly, there are limited chances that they will be submitted to additional long-term tests, given the dramatic reduction in the number of independent laboratories interested in carrying out long-term bioassays, which, with a few conspicuous exceptions, are at present almost exclusively in the hands of commercial laboratories or of laboratories internal to industries.

NO EASY SOLUTIONS FOR SITUATIONS TYPE 2B

There are no easy solutions for situations that can be defined as type 2B, when the experimental and epidemiological data are relatively limited and do not reach the level of evidence that is defined as sufficient. Group 2B includes agents that are quite disparate in terms of public health and economic relevance as well as in the level of evidence for their toxicity. Some should undergo indepth investigation without delay, such as acetaldehyde, acrylonitrile, gasoline, bitumen, chloroprene, carbon tetrachloride, 1,2-dichloroethane, hexachlorobenzene, and a few agents that were recently downgraded from group 2B to group 3 that include atrazine, phthalates, rock wool, and glass wool.

If the validity of the precautionary principle is not accepted, type 2B situations will create an impasse of which the only outlet is the official perpetuation of risk conditions with possible ominous consequences on health. In practical

terms, such situations are as difficult to deal with as those related to exposures to very low doses of recognized human carcinogens. However, admitting such difficulty does not mean that we can deny *a priori* their possible etiological role. The actual role of a long series of risk factors in increasing the cancer burden is still poorly known, and the noxious effects of low or very low concentrations of environmental pollutants have only begun to be elucidated. The adverse effects of extremely low doses of agents that act as endocrine disruptors have raised the greatest attention, such that even a newspaper like *The Wall Street Journal* expressed some concern about exposure to bisphenol A, phthalates, and atrazine.[30]

ROLE OF LOW CONCENTRATIONS

Cadmium, which was recognized as a human carcinogen after relatively high occupational exposures, represents a different spectrum of adverse effects. Considered to be a nongenotoxic carcinogen, at extremely low doses was shown to be mutagenic without causing direct DNA damage but by interfering with the mismatch repair system of DNA replication errors.[31,32] At concentrations that can be found in the general environment, cadmium can thus induce genomic instability, which is not sufficient *per se* to cause neoplastic transformation but is sufficient to increase cellular susceptibility to other exogenous and endogenous agents, possibly contributing in this way to increasing the risk for cancer.

Other examples of the long-term adverse effects of exposure to low concentrations of environmental agents include the possible prenatal origin of certain childhood leukemias. Translocations typical of myeloid leukemia, probably due to maternal exposure to some toxic compound, were shown to be present at birth in children who developed the disease years later. While not sufficient *per se* to cause the disease, they might increase the risk for leukemia by inducing genomic instability.[33,34] Furthermore, an association has been reported between maternal exposure during pregnancy and paternal exposure before conception to a series of chemicals and *Ras* proto-oncogene mutations in children who later develop lymphocytic leukemia,[35] while prenatal and early postnatal exposure to atmospheric pollutants has also been reported to be associated with an increased risk for childhood cancer.[36,37]

OUR RESPONSIBILITY

One of the priorities of research today is the unraveling of the complexity of gene–environment interactions in modulating the susceptibility to chronic diseases. We may expect that substantial progress will be made when it is possible to reliably measure both environmental exposures and genetic variations.[38] Up

to now, much more attention has been paid to the study of the individual's genome than to the measurement of individual's environmental exposures; the methodology developed for genotyping is presently far more advanced and accurate than the methodology employed in the measurement of environmental exposures.[39] To compensate for this disparity, an increased effort to upgrade exposure assessment procedures is essential. At the same time, however, we should never forget that uphill to the measurement of exposures, a key role in the protection of public health will be played by an action aimed at banning or sharply decreasing the presence of noxious chemical in our environment.

If we really want to draw up a credible table of attributable risks and, above all, if we want to implement efficient primary prevention, conscious of the responsibility we have toward the present but also future generations, we should seriously consider all the various components of risk that have until now been unjustifiably underestimated or ignored.

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