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# ENVIRONMENTAL CANCER RISK FACTORS

## A review

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**Abstract**

The risk of cancer in humans is increased by a wide spectrum of factors, which ranges from exposure to an identified agent, such as environmental chemicals or a virus, to a culturally determined behaviour, such as smoking, or to socio-economic conditions. We are today able to intervene on some of these factors, while others affect risk by as yet undetermined pathways. Only progress in the understanding of the mechanisms by which these factors act can lead to specific means of cancer prevention. There is no compelling reason to believe that the number of carcinogenic agents, to which humans can be exposed, is infinite, nor is it unreasonable to assume that it will eventually be possible to identify most of them. The variety of cancer risk factors of which we are presently aware implies, however, that it would be impossible to have just one simple approach to cancer control and cancer prevention. It is rather encouraging that the applicability of new laboratory methods to epidemiological surveys seems to open the way to a laboratory-integrated epidemiology.

*Key words:* Human cancer; risk factors, epidemiology, prevention, review.

### Regional differences in cancer incidence

Cancer incidence and cancer mortality vary considerably not only between the large areas of the world, but also between different areas within most countries, probably because political boundaries rarely, if ever, enclose a population that is genetically, culturally and socio-economically homogeneous, within an environmentally homogeneous region.

As Parkin et al. (18) have confirmed recently, this variation is reflected not only in the absolute frequency of cancer, but also in the different preponderant target sites.

The considerable variations among the different regions of the world (Table 1) provide a clear indication that different public health priorities may exist in different countries. For instance, the most frequent cancer in developing countries is cancer of the cervix, which ranks only 10th in developed countries. In the latter, lung cancer predictably ranks first, while it ranks 6th in the developing countries. With the increasing spread of the smoking habit and of intense urbanization, it can be easily and sadly predicted that, unless efficient preventive measures are taken rapidly, lung cancer incidence will increase sharply in developing countries in the near future.

Considerable differences in tumour incidence also occur within Europe, although they are smaller than at the world level. This is to be expected for several reasons, among which is the narrower spectrum of cultural, socio-economic and environmental differences than at the world level. While genetic factors will contribute to differences in risk in Europe as everywhere in the world, it is very unlikely that they will play a role of the same importance as, for instance, skin colour has for the observed differences in risk of skin tumours between black and white populations living in the same environment. It can therefore be expected that the differences in incidence observed in various parts of Europe above a certain common background may, to a considerable extent, be related to environmental factors.

Leaving aside for a moment our knowledge of causal factors, an estimate of the reduction of incidence of cancer that could be achieved in a given population can be derived from the differences between the highest and lowest observed risks, for a given organ, in populations that are genetically not too dissimilar. Thus, achievement of the lowest rates observed in populations for which a reliable cancer registry exists would seem a suitable goal for primary prevention efforts. This would imply that within Europe, a reduction could be achieved for gastric

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cancer in males from 43.7 to 11.5 per $10^5$ (a reduction of 74%); for large bowel cancer from 44.0 to 12.1 (a 72% reduction); for lung cancer from 110.4 to 24.5 (a 78% reduction); bladder cancer from 24.7 to 7.7 (a 69% reduction); and for breast cancer, from 72.2 to 16.2 (a 77% reduction). The total reduction of incidence that is theoretically achievable in Europe, if calculated on the incidence of all cancers, could thus be from the present maximum rates between 330 and 240 per $10^5$ per annum to rates between 164 and 105 cases per $10^5$ per annum, incidences calculated by adding the lowest incidence observed in Europe for each site (Table 2).

Among the cancers the incidence of which could be reduced by primary prevention are also childhood cancers. The incidence of childhood cancers does not vary as much as adult cancers, but it is certainly not homogeneous worldwide. This does not, in other words, represent the unavoidable baseline incidence of human tumours. There are, for instance, considerable differences in the incidence of Wilms' tumour as well as of acute lymphocytic leukaemia in different regions of the world (19). It would seem logical to assume that a genetic component plays an important role in the origin of tumours that appear early in life, and for some a genetic origin is recognized, as for instance for bilateral retinoblastoma. There are good grounds for assuming, however, that childhood cancer can to some extent also be related to environmental factors, even if their action in most cases is, by definition, much more rapid than in the case of adult tumours. Exposures to environmental factors may, however, begin prenatally, as the instances of prenatal exposure to x-rays (23) or to DES (9) demonstrate.

**Table 1**

*Ranking of the most frequent cancer target sites in developed and developing countries. (From ref. 18 (modified))*

| Developed countries | Developing countries |
|---|---|
| 1. Lung | 1. Cervix |
| 2. Colon–rectum | 2. Stomach |
| 3. Breast | 3. Mouth–pharynx |
| 4. Stomach | 4. Oesophagus |
| 5. Prostate | 5. Breast |
| 6. Bladder | 6. Lung |
| 7. Lymphoma | 7. Liver |
| 8. Mouth–pharynx | 8. Colon–rectum |
| 9. Corpus uteri | 9. Lymphoma |
| 10. Cervix | 10. Leukaemia |

Of the 6.35 million new cancer cases occurring in the world in 1980: 49.3% occurred in developed countries (population: 1 135.9 millions) and 50.7% occurred in developing countries (population: 3 214.4 millions)

**Table 2**

*Reduction in cancer incidence rates (age-standardized per $10^5$ population) theoretically achievable in Europe*

| Site | Maximum incidence | Minimum incidence | Percentage of reduction |
|---|---|---|---|
| Stomach | 43.6 | 5.7 | 74 |
| Large bowel | 44.0 | 12.1 | 72 |
| Lung | 110.4 | 24.5 | 78 |
| Bladder | 24.7 | 7.7 | 69 |
| Breast | 72.2 | 16.2 | 77 |
| All sites | 330–240 | 164–105 | 50–68 |

## Environmental and host factors

A cumulative cancer incidence approaching 100% can be observed when levels of exposure to a carcinogenic agent are so high as to produce effects which bypass any possible natural (genetic) resistance, and when susceptibility to an environmental carcinogen is greatly increased, or resistance is greatly decreased, by an inborn defect. An example of the first situation is the nearly 100% cumulative incidence of bladder cancer in workers following prolonged occupational exposure to aromatic amines (29). An example of the second situation is the very high incidence of skin tumours occurring at a young age in xeroderma pigmentosum (XP) patients who have a defective capacity to repair DNA damage caused by UV light (6, 24). Both the exposure of presumably healthy individuals to man-made carcinogens, and the exposure of individuals with genetically impaired resistance to ubiquitous carcinogenic agents can therefore result in a greatly elevated cancer risk. However, relatively few cancer cases are the result of such extreme situations.

Most patients who die from cancer die because of a single tumour (much more rarely because of multiple tumours), but only a still ill-defined proportion of them can be related causally to exposure to a single identified carcinogenic agent. Tobacco smoke is certainly not the least important example of a complex mixture of initiators, promoters and modulators of progression, of which the individual actions cannot be clearly distinguished. A considerable proportion of human cancers are thus probably related to exposure to a variety of carcinogenic agents, which act together, in sequence and with the participation of agents that modify stages of the carcinogenic process.

There is no compelling reason to believe that the number of carcinogenic agents to which humans can be exposed is infinite, nor is it unreasonable to assume that it will eventually be possible to identify most of them. What has been more difficult to prove is the fact that an agent that has been shown to be carcinogenic at relatively high levels, is also carcinogenic at much lower exposure levels, either alone or in combination with other factors, also present at very low levels.

In addition to an extensive gradation of levels of exposure to man-made, naturally occurring and endogenous chemical carcinogens, viruses and radiation, there is a

**Table 3**

*Cancer factors. (From ref. 10 (modified))*

| Category | Example |
|---|---|
| Genetic predisposition | Xeroderma pigmentosum |
| Chemicals | Benzene |
| Industrial processes | Rubber industry |
| Hormones | Oestrogen replacement therapy |
| Immunosuppression | Organ transplantation |
| Ionizing radiation | Therapeutic x-ray |
| Other radiation | Ultra-violet B |
| Viruses and infectious agents | Hepatitis B virus |
| Culturally determined habits | Tobacco smoking |
| Therapeutic regimens | Cyclophosphamide |
| Diet | Excess caloric intake |
| Socio-economic conditions | Less-favoured occupational class |

gradation of genetic susceptibility or resistance to the mutagenic and otherwise damaging effect of environmental and endogenous noxious agents. The interplay of environmental and host factors is not necessarily limited to the early stages of carcinogenesis and probably also extends over the late stages of promotion and progression.

### The variety of cancer risk factors

The variety of cancer risk factors of which we are aware (Table 3) (10) also clearly implies that it would be impossible to have just one single approach to cancer control and cancer prevention. We could, however, try to indicate where preventive measures could on the one hand be feasible, and on the other most effective.

Clearly, prevention is feasible in relation to chemicals, industrial processes, medical drugs, hepatitis B virus, to a certain extent radiations, and certainly, even if resistance has been found greater than expected, in relation to the habit of smoking. At the same time, socio-economic conditions can also be improved. Sigerist (22) wrote, over 30 years ago, that poverty had been and still was at that time the chief cause of disease. In developing countries the situation is not much different from what it was then, and may even have deteriorated, while in developed countries there have been changes in certain characteristics of what is called poverty (2, 28).

Although recent advances in molecular genetics may make it conceivable for us to directly modify the individual genetic conditions predisposing to cancer, this possibility is still far from realisation. For the present, we hope being able to understand why some individuals are at a greater risk than others of developing a clinical cancer, but even this will not decrease the importance of identifying and eliminating or decreasing exposures to carcinogenic agents.

### The known causes of human cancer

The approaches used to identify carcinogenic factors have, to a certain extent, determined the types of agents that have so far been discovered. Both the epidemiological and the experimental approaches suffer from serious limitations, largely related to our incomplete knowledge of the mechanisms of carcinogenesis. Epidemiology did not, until recently, permit discrimination between a true and false effect unless an exposure increased the risk of cancer by at least 20–30% above that seen in controls. For this reason carcinogenic factors that may produce a smaller increase in risk than that produced by some human carcinogens already known might remain undetected, even though they could pose a serious public health problem because of the large numbers of people affected. The experimental approach suffers from the limitation that there are no satisfactory criteria for directly extrapolating from experimental animal data to the human situation.

Another impediment to the application of these two approaches has been the fact that for a long time epidemiologists and experimentalists (and also clinicians) have gone their own way without any attempt to integrate their knowledge and competence in a truly multidisciplinary approach. The lists of carcinogenic agents that can be prepared today must therefore be considered provisional and incomplete. Industrial processes, chemicals and groups of chemicals for which exposures have been mostly occupational, drugs causally associated with cancer in humans, and environmental and culturally determined factors, for which a causal relationship with human cancer has been established, are presented for convenience in separate lists in Tables 4, 5, 6 and 7. In Table 8 are listed risk factors for which an association but not a causal relationship with human cancer has been established. These lists are largely derived from the IARC Monographs (11, 12).

### The role of dietary factors

In keeping with the increasing attention paid in recent years to lifestyle and behaviour as risk factors for human cancer, it was to be expected that the role of the oldest lifestyle factor, namely eating, would become prominent and, almost unavoidably, fashionable. However, in spite of the great interest in the role of nutrition in the origin of human cancer, it is still not possible to make but vague recommendations concerning a safe diet.

It was suggested that the ideal diet might have been that which the ancestors of homo sapiens learned to choose during the millions of years before agriculture, when, as food collectors and hunter-gatherers, they had to adapt to what was available and within reach. The pre-agricultural diet was possibly more varied than has been assumed for some time, and data from archaeological studies indicate consistently that nutritional diseases were rare before agriculture was introduced. In the more recent period some

**Table 4**

*Industrial processes causally related to human cancer. (From ref. 12)*

| Exposure | Target organs |
|---|---|
| Aluminium production | Lung, bladder (lymphoma, oesophagus, stomach) |
| Auramine, manufacture of | Bladder |
| Booth and shoe manufacture and repair (certain occupations) | Leukaemia, nasal sinus (bladder, digestive tract) |
| Coal gasification (older processes) | Skin, lung, bladder |
| Coke production | Skin, lung, kidney |
| Furniture and cabinet making | Nasal sinus |
| Haematite mining, underground, with exposure to radon | Lung |
| Iron, steel and steel founding | Lung (digestive tract, genito-urinary tract, leukaemia) |
| Isopropyl alcohol manufacture (strong acid process) | Nasal sinus (larynx) |
| Magenta, manufacture of | Bladder |
| Rubber industry (certain occupations) | Bladder, leukaemia (lymphoma, lung, renal tract, digestive tract, skin, liver, larynx, brain, stomach) |

(Suspected target organs in parentheses)

**Table 5**

*Chemicals and groups of chemicals causally related to human cancer for which exposure has been mostly occupational. (From ref. 12)*

| Exposure | Target organs |
|---|---|
| 4-aminobiphenyl | Bladder |
| *Arsenic and arsenic compounds | Skin, lung (liver, haematopoietic system, gastrointestinal tract, kidney) |
| Asbestos | Lung, pleura, peritoneum (gastrointestinal tract, larynx) |
| Benzene | Leukaemia |
| Benzidine | Bladder |
| Bis(chloromethyl)ether and chloromethyl methyl ether (technical grade) | Lung |
| *Chromium compounds, hexavalent | Lung (gastrointestinal tract) |
| Coal-tars (and iatrogenic exposures) | Skin, lung |
| Coal-tar pitches | Skin, lung, bladder |
| Mineral oils (untreated and mildly treated) | Skin (respiratory tract, bladder, gastrointestinal tract) |
| Mustard gas | Lung (larynx, pharynx) |
| 2-naphthylamine | Bladder |
| *Nickel and nickel compounds | Nasal sinus, lung (larynx) |
| Shale-oils | Skin (colon) |
| Soots | Skin, lung |
| Talc containing asbestiform fibres | Lung (pleura) |
| Vinyl chloride | Liver, lung, brain, lymphatic and haematopoietic system (gastrointestinal) |

* The evaluation of carcinogenicity to humans applies to the group of agents as a whole and not necessarily to all individual agents within the group.
(Suspected target organs in parentheses.)

10 000–6 000 years ago, in a fundamental transformation of this most important aspect of our lifestyle, made possible by the progressive domestication of plants and animals (3), humans started to become food producers (5). Like baboons, humans apparently have a good capacity for dietary adaptation; our preferences for, as well as the exclusions of, certain foods are probably dictated more by cultural pressures than genetically determined (4). As a consequence of the introduction of agriculture, the human diet underwent a fall in the proportion of proteins and fat consumed, and a rise in the proportion of carbohydrates. In addition, it contained less calcium and was probably deficient in some of the B-group vitamins (31).

A second major change in nutritional habits occurred about two centuries ago, as a result of the industrial revolution. A wider range of nutritionally desirable food became available, in quantities that were not obtainable before, to at least part of the world's population, and this certainly contributed to the increase in life expectancy. In recent decades, food production in industrialized countries has undergone a further very considerable increase, but at the same time a high proportion of nutritionally undesirable but palatable food has also become available (31). In pre-agricultural times, to eat what one liked meant to eat what one needed; in modern times, this is only very rarely, if ever, true. In addition, humans, in spite of the ease with which they culturally adapt to new food, have not completely evolved towards total acceptance of food introduced with the adoption of agriculture. There is, for instance, still a diffuse intolerance to cereals and more so to milk consumed after weaning.

Lactose is metabolized only by the intestinal epithelium, where the enzyme lactase is located and from which it gradually disappears after a maximum of activity in the perinatal period (14). Most of the human adult populations of the world follow a pattern similar to that of other mammals, viz. losing the capacity for lactose digestion shortly after weaning. In our dairy-oriented culture, the individuals who are intolerant to lactose have been generally seen as deviant, while the contrary is actually true, since it is the lactose digester who is the deviant. The high prevalence in certain populations of individuals maintaining the capacity of lactose digestion during adulthood has been attributed to nutritional selective pressure which may have operated within a relatively short period (certainly not more than 10 000 years) among the descendants

**Table 6**

*Drugs causally associated with cancer in humans. (From ref. 12)*

| Exposure | Target organs |
|---|---|
| Analgesic mixtures containing phenacetin | Renal pelvis (ureter, bladder) |
| Azathioprine | Lymphoma (skin, hepatobiliary system, mesenchymal tumours) |
| Clorambucil | Leukaemia |
| Chlornaphazine | Bladder |
| 1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (Methyl-CCNU) | Leukaemia |
| Cyclophosphamide | Bladder, leukaemia |
| Diethylstilboestrol | Cervix, vagina, breast (testis) |
| Melphalan | Leukaemia |
| 8-Methoxyproralen plus ultraviolet radiation | Skin |
| MOPP and other combined chemotherapy, including alkylating agents | Leukaemia |
| Myleran | Leukaemia |
| Oestrogen replacement therapy | Endometrium (breast) |
| *Oestrogens non-steroidal | Cervix, vagina, breast (testis) |
| *Oestrogens steroidal | Endometrium (breast) |
| **Oral contraceptives, combined | Liver |
| Oral contraceptives, sequential | Endometrium |
| Treosulfan | Leukaemia |

* The evaluation of carcinogenicity to humans applies to the group of agents as a whole and not necessarily to all individual agents within the group.
** There is also conclusive evidence that these agents protect against cancer of the ovary and endometrium.
(Suspected target organs in parentheses)

**Table 7**

*Environmental and cultural risk factors causally associated with human cancer*

| Exposure | Target organs |
|---|---|
| Erionite* | Pleura |
| Ionizing radiations** | Leukaemia, skin, various internal organs |
| UV light** | Skin |
| Aflatoxins* | Liver |
| Alcoholic beverages* | Oral cavity, pharynx, larynx, oesophagus, liver (breast) |
| Betel-quid chewing with tobacco* | Oral cavity (pharynx, larynx, oesophagus) |
| Smokeless tobacco use (chewing and oral snuff)* | Oral cavity (pharynx, oesophagus) |
| Tobacco smoke* | Lung, bladder, oral cavity, larynx, pharynx, oesophagus, pancreas, renal pelvis (stomach, liver, cervix) |
| Hepatitis B virus infection** | Liver |
| Human T-cell leukaemia virus** | T-cell leukaemia |

(Suspected target organs in parentheses)

* From ref. 12.
** Not yet evaluated in the IARC Monographs programme.

**Table 8**

*Risk factors for which an association but not a causal relationship with the occurrence of human cancer has been established*

| Agent | Site |
|---|---|
| Papilloma virus | Cervix uteri (other sites) |
| Epstein-Barr virus | Rhinopharyngeal carcinoma<br>Burkitt's lymphoma |
| Schistosoma haematobium | Urinary bladder |
| Clonorchis sinensis | Liver |
| *37 chemicals (+ 162 chemicals) | Various sites |
| Dietary related factors | Various sites |

* Groups 2A (and 2B) in: Ref. 12

of ancestors who kept lifestock and were possibly the first to adopt the habit of producing dairy products (16). If, and to which extent, tolerance and intolerance to lactose may be related to a different risk for colon cancer is unknown.

The proportion of human cancers that could be directly or indirectly related to dietary factors is high, at least if we consider the cancer sites for which such a relationship is conceivable. This is one good reason why primary prevention of cancer through dietary intervention exerts an obvious attraction, and several intervention trials are currently under way in different parts of the world. The possibilities are made even more attractive by the fact that not only might we avoid exposure to carcinogens present as such in the diet or formed endogenously from what we eat, but also that certain dietary factors may protect against cancers caused by exposures to other, non-dietary factors. The risk derived from being exposed to a carcinogenic agent, however, is generally greater than that from not being exposed to a protective factor. While it is highly unlikely that we can develop an anti-cancer diet, we can, even on the basis of the present knowledge, recommend the avoidance of excessive caloric and fat intake, avoidance of mycotoxin-contaminated food, limitation of the intake of alcoholic beverages, regular consumption of fresh vegetables and fruit, and the inclusion of a reasonable amount of fibre in our diet (8, 21).

Even if kept at a very broad level, recommendations on the diet may contribute significantly to the reduction of certain risks. Similarly, the improvement of socio-economic conditions may also contribute, by means that we are still unable precisely to quantify, to the reduction of cancer risks and cancer mortality.

**Table 9**

*Relative risks for cancer associated with certain exposures. (From ref. 13 (modified))*

| Organ affected | Factor | High risk level | Low risk level | Reported relative risk |
|---|---|---|---|---|
| Breast | Ionizing radiations | 1 Gy | No exposure | 3.0 |
| Bladder | Cigarette smoking | 25 cigs./day | Non-smokers | 5.0 |
| Leukaemia | Benzene | Occupational exposure | No occupational exposure | 5.6 |
| Lung | Cigarette smoking | 25 cigs./day | Non-smokers | 30 |
| Liver | Hepatitis B virus | Chronic carriers | Non-carriers | 100 |
| Pleura, peritoneum | Asbestos | Occupational exposure (mainly crocidolite) | No occupational exposure | 500 |
| Bladder | Benzidine and/or 2-naphthylamine | Occupational exposure | No occupational exposure | 500 |

### Estimating the impact of preventive measures

When a preventive measure is proposed we should always bear in mind that a clear dichotomy between exposed and non-exposed individuals rarely exists and that in most instances, and for most agents, there will be gradations of exposure from minimal to moderate to very high. If we want to justify an intervention activity and possibly quantify its effects, it is important to remember that the intervention will generally not eliminate exposure completely (except in certain specific situations, such as the use of carcinogenic chemicals in the workplace or the use of certain carcinogenic drugs). More often, the intervention will result in a global decrease of the exposure levels. If we take the example of dietary-related factors, we can reasonably aim at some moderate, widespread decrease in risk and/or increase in protection, rather than a drastic and absolute effect. Any attempt to evaluate the possible impact of preventive measures must take into account several factors besides their actual feasibility, prominent among which are both the number of subjects at risk and the magnitude of the risk. A few examples of relative risks due to exposure to known carcinogenic agents are given in Table 9. Considering the variety of risk factors in relation to which intervention is possible, we may thus try to estimate the proportional decrease in risk from which exposed individuals might benefit if these risk factors were eliminated, although without forgetting that the measurement of the relative risk does not allow the effect on the whole population to be calculated. The overall reduction in the population rate of the disease is also dependent on the proportion of the population that is exposed (13).

Furthermore we must not forget the fact that the effect of a preventive measure aimed at reducing the incidence of a chronic disease, such as cancer, is never immediate. The time lapse between the adoption of a preventive measure and its beneficial effect may be very long, but in certain instances, such as smoking cessation, it can be relatively short.

### The role of prenatal events

The clinical manifestation of cancer is the end-point of a very long process. It may take 40 years for a mesothelioma to appear, following exposure to asbestos; it takes between 20 and 40 years for a lymphoma to appear, following infection with HTLV-1. Similarly, an increased risk for solid tumours of certain sites may become apparent decades after irradiation.

The observations at Hiroshima and Nagasaki indicate, for instance, that an increased risk of lung cancer did not reveal itself in individuals who were young at the time of the explosion until after 30 years or more (15). It was recently reported that an increased risk of solid tumours at multiple sites has become apparent lately in the progeny of women who were pregnant at the time of the atomic explosion (14). Epidemiological studies aimed at detecting effects appearing after such a long delay would present very considerable difficulties, and in fact only the very intense and continuous surveillance in Hiroshima and Nagasaki made it possible to detect the relationship between an event which occurred 40 years ago and the increase in cancer incidence at various sites.

Experimentally, it has been shown that the prenatal exposure of fetuses to DMBA induced the same mutation that was specifically identified in skin tumours produced in adult mice. This mutation, which occurred in only one allele of the c-Ha-*ras* gene, is probably a critical event in the development of the tumour, but alterations in the apparently normal allele may also be necessary before neoplasia occurs (30). Cells harbouring an oncogene activated by a point mutation may therefore lie dormant, unless and until they are exposed to a promoter agent which then becomes the critical factor in the development

of malignant tumours. Further experimental confirmation of this fact has come from experiments on transgenic mice, where it was shown that the early appearance of tumours is related to the presence of a deregulated oncogene, in this case a c-*myc* transgene, but that the presence of the c-*myc* transgene is not on its own a condition sufficient for the development of a tumour (17).

This epidemiological and experimental evidence indicates that a prenatal exposure to carcinogenic agents may cause not only the induction of tumours early in life, but also an increased cancer risk surfacing late in life, presumably only after prolonged exposure to low doses of carcinogens and/or to promoting agents. We should therefore consider the possible consequences of environmental exposures for subsequent generations (25).

### The rise of a new epidemiology

The gap between experimental results and hypotheses that can be proven or even just investigated by epidemiologists has until recently been very considerable. It is, however, quite encouraging that the development of methods for measuring low levels of exposures has occurred parallel to progress made in understanding the process of carcinogenesis, and in the applicability of new laboratory methods for epidemiological surveys. While the 'easy time' for epidemiologists seems to be over, a new era of laboratory-integrated epidemiology is beginning (1, 7, 20, 26, 27).

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