Environmental Causes of Cancer

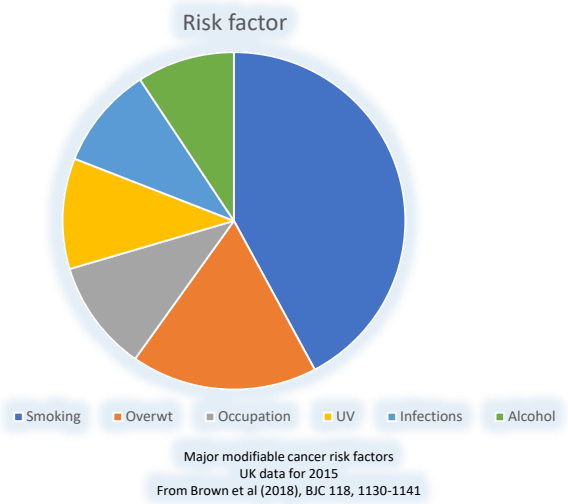
What is cancer?

Cancer is the uncontrolled replication of cells. Such cells have different characteristics from regular cells, enabling them to escape the normal mechanisms controlling cell division and fate. Cancer develops when cells progressively acquire several of these characteristics.
Cancer is a major cause of morbidity and mortality throughout the world. During their lifetime, approximately 50% of the population will develop cancer and, globally, almost 17% will die of cancer. Cancer is spoken of as if it were a single disease, but it is a multiplicity of diseases, each with its own aetiology, risk factors and population trends. Nevertheless, amongst adverse health effects, it is amongst those diseases treated with most dread, not surprisingly given that some forms of cancer are untreatable and have a very high mortality rate.

Cancer is a progressive and persistent disease and it typically takes approx. 25% of a lifespan to develop cancer in a solid tissue, such as the liver or lung. A corollary of this is that most cancers are diseases of older age, and almost 50% of cancer deaths are in the over 70s. Hence, as the population ages, the proportion dying of cancer increases. This, in part, reflects the effectiveness of improving population longevity.

Given the above, there has been intense focus over the last 50 years in trying to identify the causes of cancer, in that prevention would be the most effective public health strategy. Early studies concluded that the majority of cancer was environmental in origin and some inferred that this was because of the presence of chemicals in the environment, whereas in fact it meant that most cancers were not obviously inherited, i.e. of genetic origin.

Chemical carcinogens



Major modifiable cancer risk factors
UK data for 2015
From Brown et al (2018), BJC 118, 1130-1141

Early epidemiological studies established some of the major avoidable causes of cancer, among which are tobacco smoking, diet, reproductive and sexual behaviour such as age at first pregnancy (Doll & Peto, 1981). A number of industrial and environmental chemicals were also shown to cause cancer in exposed subjects, particularly in occupational settings. These included some heavy metals such as cadmium, polycyclic aromatic hydrocarbons, such as coal and in oil deposits, and aromatic amines, such as benzidine. Often the specific chemical responsible could not be identified, as exposures were almost always mixed.

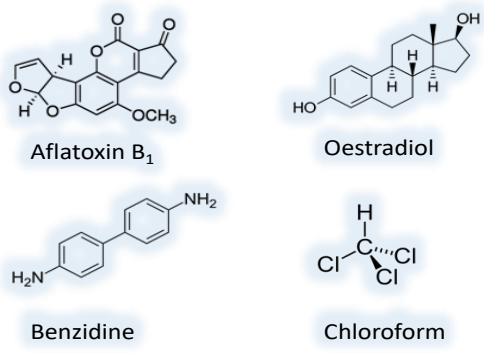
In early investigations trying to identify the major chemical causes of cancer, a number of substances were shown to be potent carcinogens in experimental animals, including those for which there was evidence of their carcinogenicity in humans, among them aflatoxin B_1, benzidine, and dimethylnitrosamine. These cause cancer through their chemical reactivity (or more usually that of a short-lived metabolite) with DNA, causing gene mutations. When it became apparent that such mutagens could be rapidly detected in a simple *in*

vitro bacterial screen (Ames Test) (Ames et al, 1975), there was hope that this would enable the prevention of a large proportion of cancer and this became a significant focus of effort.

Biological basis for the identification of chemical carcinogens

In parallel with the development of short-term tests for genotoxicity, the US National Toxicology Program started systematic carcinogenicity testing of chemicals in rodents. Whilst a number of compounds that were clearly carcinogenic were also strongly mutagenic, it soon emerged that many chemicals that induced cancer in experimental animals did so by a mechanism other than through direct interaction with DNA. These became known as non-genotoxic carcinogens (Ames & Gold, 1990). Advances in cancer biology revealed that, in general, anything that increased the rate of cell division or that reduced the rate of cell death, increased the probability of cancer developing in animals.. This was through either the emergence of spontaneous mutations or the expression of phenotype of pre-existing mutations. This led to the concept of a mode of action, whereby a series of key events was necessary for cancer to develop. These exhibit dose and temporal dependency and hence, cancer (at least that by a non-genotoxic mode of action) does not develop until exposure exceeds a certain dose level, and until after a certain time. Before that, the process is reversible. Further, a number of the key events involved are species-specific, so that some modes of action in rodents are not relevant to humans (Boobis et al, 2006).

Identification of chemical carcinogens



Some genotoxic and non-genotoxic natural and synthetic chemical carcinogens

The lifetime cancer bioassay is still considered by many as the gold standard for identification of chemical carcinogens. However, there is now a recognition that the outcome needs to be considered as part of an overall assessment of the weight-of-evidence. This would include information on the mutagenicity of the compound, particularly DNA-reactive gene mutation, immunosuppressive properties, and whether the compound increases cell proliferation, such as steroid hormones, which can act as growth factors. Epidemiological studies can also be invaluable, but when conducted in environmentally-exposed populations there are a number of key considerations that need to be taken into account. Amongst these, exposure assessment is usually the most problematic as individuals are not exposed to single substances and often exposure to several chemicals is co-associated. For example, in studies of pesticides, members of the general public will be exposed to trace amounts of multiple active substances (pesticides), as well as co-formulants. However, the analysis is even more complex, as those most likely to be exposed to pesticides will be those who consume most fruit and vegetables. There is evidence that a balanced diet rich in fruit and vegetables can reduce the risk of some forms of cancer. But there may also be increased exposure to naturally occurring carcinogens, such as aflatoxin B_1 found in certain nuts due to fungal contamination. Such eating patterns may also be associated with other lifestyle factors, leading to differences in exposure pattern from those with a low fruit and vegetable diet. During the processing of food, natural constituents may be chemically transformed to produce chemical carcinogens, such as acrylamide formed during cooking of starchy food and heterocyclic aromatic amines formed during the grilling/barbecuing of meat. There are a number of monitoring programmes in place globally, in which levels of chemicals in different media are measured, to help understand exposure potential in different populations.

There are techniques in epidemiology to take account of these potentially confounding factors, but this emphasises the difficulty in reaching conclusions on causation. It was for this reason that Bradford Hill (1965) laid out a series of considerations when attempting to determine causation in epidemiological studies. Among these considerations are magnitude of exposure, dose-response, temporal consistency, biological plausibility and experimental support. Hence, the risk assessor today will take all of this into account, including mode of action, if known, and potential human relevance of experimental observations, in reaching a conclusion on the carcinogenic potential of a chemical.

While there is much concern about the possible contribution of environmental chemicals to cancer, from a public health perspective, this is a minor factor. It is clear that the current major causes of cancer are cigarette smoking, which is still the major contributor although declining, diet, obesity, which are to some extent inter-related, radiation, viral infections, air pollution and occupation. Some of the causes of occupational cancer will be chemical exposure, but other factors are involved, such as UV radiation. This does not mean that all due steps should not be taken to ensure that the population is not unduly exposed to carcinogenic chemicals, but in debating policy it is important to consider relative risks. A good example of this can be seen in the debate about the use of e-cigarettes. While these are not without risk, it is clear that switching from conventional cigarettes to e-cigarettes could appreciably reduce the harm from smoking conventional cigarettes (COT, 2020).

Future developments

The recognition that cancer is a multi-stage process and that it can come about in many different ways is leading to a more mechanistic approach to the identification of potential causes of cancer, than the hitherto empirical approaches in use to date. Potent DNA-reactive carcinogens are now rarely encountered *de novo*. Those producing chemicals, such as pesticides, food additives, human medicines, make every effort to design out structural characteristics responsible for DNA reactivity. Short term tests for mutagenicity are relatively effective in identifying potential DNA-reactive chemicals. Hence, any contribution of environmental chemicals to cancer is now largely by mechanisms involving other than DNA-reactive gene mutation. Strategies to identify such chemicals must take this into account. Hence, more consideration needs to be given to likely human exposure and to the evaluation of pre-neoplastic key events, using mode of action as a foundation. This means that lifetime cancer bioassays in rodents will not be necessary. The long term goal would be to replace even shorter term studies in experimental animals with new approach methodologies (*in silico* and *in vitro*) but this will depend on the extent to which such methods can be developed and provide reliable information on the necessary key events to permit assessment of potential adverse outcomes in exposed individuals.

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