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COMMENTARY

Nature and nurture: possibilities for cancer control

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Nature and nurture interact and in most cases it is impossible to specify quantitatively the contribution of either to the causation of a disease. Only rarely is either neutral in the sense that the other accounts for all the variation in risk. It seems unlikely that more than a few per cent of all cancers will be accounted for by inherited susceptibility with a high penetrance and a neutral environment. Small variations in susceptibility may, however, be associated with different genetic alleles that will facilitate focused measures of prevention and perhaps provide a lead to causation. For the practical control of most cancers we must intervene by treatment or prevention. Knowledge of the variation in the incidence of cancers suggests that age-specific incidence rates could be reduced by 80–90%, half by the application of existing knowledge. The possibilities of control by prevention are discussed under the headings of tobacco smoke, alcohol, infection, diet, physical activity, reproduction, medicines and medical procedures, and occupation and pollution. In conclusion, attention is drawn to eight types of cancer that have become more common in the UK in the last 25 years, some of which we do not know how to prevent and which require urgent research.

Introduction

In 1933, Lancelot Hogben, then Professor of Social Biology in the University of London, gave a series of lectures on the methods of clinical genetics, which were subsequently published in book form under the title of *Nature and Nurture* (1). At that time, it was common to think of disease as being either genetic in origin or due to some agent in the environment but that, if both played a part, as they obviously did in determining many human characteristics such as stature and blood pressure, it was somehow possible to apportion responsibility in simple quantitative terms and allocate x% to heredity and $(100 - x)$% to external (or environmental) influences. This, Hogben showed, was scientific nonsense: the contribution of each varied with circumstances. Occasionally, the relationship between the two was such that either the environment or heredity could be said to be neutral, the other accounting for the whole of the observed variation; but usually, they interacted with each other, the importance of one depending on the condition of the other.

Hogben was primarily concerned with the debate about the factors that determine intellectual capacity and his analysis led him to conclude that 'In so far as a balance sheet of nature and nurture has any intelligible significance, it does not entitle us to set limits to changes that might be brought about by regulating the environment'. Now, 60 years later, Hogben's thesis is standard biological teaching and his conclusion may seem somewhat banal. It was important, however, at the time, because of the enthusiasm that was then commonly expressed for eugenic solutions to the social problems of the day, and it is important now in relation to the control of cancer, to which it is equally applicable, for the dramatic discoveries of molecular biology could engender a sort of neo-eugenic attitude to the control of the disease.

Control of nature

As specific genetic abnormalities become known, it is evident that a few cancers can be avoided by selective abortion or by ablation of the organ at risk, indicated (if appropriate) by the results of regular screening. These include the cancers listed in Table I, all of which appear in childhood and must be expected to occur in 90% or more of the carriers of the genes. To these we must add the breast and ovarian cancers that occur later in life in carriers of the *BrCa 1* and *2* genes, the colon cancers associated with defects of the DNA repair genes, *hMS2* and *hML1*, and the cancers associated with several mutated genes when present in double dose. The list will certainly grow, but I doubt whether more than a few per cent of the cancers that now occur in a population will be accounted for by inherited susceptibility with a high penetrance and an essentially neutral environment.

What may be more important is the discovery of genetic alleles that increase to a small extent an individual's susceptibility to an external carcinogen. These could be more common and may facilitate focused measures of prevention, emphasizing, for example, the risk of skin cancer from UV light in people with light coloured skin and, perhaps, the risk of lung cancer in smokers with some alleles of *CYP* genes (1A1 and 2D6) that metabolize aromatic hydrocarbons and debrisoquine. Knowledge of such alleles may, moreover, in some circumstances

Table I. Cancers attributable to inherited susceptibility with high penetrance

Syndrome	Principal sites of tumours	Gene
Retinoblastoma	retina	*RB1*
Familial adenomatous polyposis	colon, rectum	*APC*
Multiple endocrine neoplasia		
Type 1	parathyroid	
	pituitary	*MEN1*
	pancreas	
Type 2	thyroid	*RET*
	adrenal	
Neurofibromatosis	acoustic nerve	*NF2*
Type 2	Schwannoma	
	meningioma	
Li–Fraumeni	breast	
	brain	*TP53*
	soft tissue	
von Hippel–Lindau	kidney	
	CNS angiomas	*VHL*
	phaeochromocytoma	
Nephroblastoma	kidney	*WT1*

Table II. Incidence of prostate cancer (age standardized rate per 100 000 men per year)

Ethnic group	US		Bermuda	Hiroshima or Shanghai
	SEER population	Hawaii		
Black	82.0	–	64.0	–
White	61.8	62.8	22.9	–
Japanese	–	34.4	–	10.0
Chinese	–	28.0	–	1.7

Table III. Incidence of chronic lymphatic leukaemia (age standardized rate per 100 000 men per year)

Ethnic group	US		Hiroshima or Shanghai
	SEER population	Hawaii	
Black	3.1	2.0	–
White	2.3	–	–
Japanese	–	0.1	0.3
Chinese	–	0.4	0.2

provide a lead to the aetiology of the disease. The example of the effect of ABO blood groups on the risk of gastric cancer is admittedly not encouraging, for it has been known for 40 years without leading to any increase in knowledge of the means by which gastric cancer is produced, but we should not assume that any other similar discovery would be equally sterile. Reichardt *et al.*, for example, have shown that substantial differences exist between the prevalence of some alleles of the 5-α-reductase gene in black Americans, white Americans and East Asians (2), and that these correlate with the differences in the incidence of prostate cancer shown in Table II. As 5-α-reductase contributes to the metabolism of testosterone, this suggests that the levels of testosterone and its metabolites play a part in the production of the disease. It is possible, however, that most of the differences could be environmental or behavioural in origin, as the rates in Japanese and Chinese in their homelands are substantially lower than the corresponding rates in Hawaii. Where there certainly does seem to be a major ethnic difference in susceptibility is in the risk of chronic lymphatic leukaemia, the incidence of which varies 10-fold between white populations in Australasia, North America and Western Europe, and Chinese and Japanese populations (3). In this case, the low incidence of the disease in Chinese and Japanese is similarly low in both their homelands and abroad (Table III).

Control of nurture

For the practical control of most cancers, however, we must intervene either by treatment, with or without screening, or prevention. Both approaches provide possibilities, but it is only the second, the control of nurture, that I propose to discuss. Its practicability has been demonstrated by the discovery of many avoidable causes and by the fact that the incidence of nearly all the common cancers varies greatly on migration from one country to another and, in stable populations, over time. If the causes responsible for this variation could be identified and controlled we could reduce the age-specific incidence of the disease by some 80–90%. Half of this could be achieved by the application of existing knowledge. Much, however, requires further research and it is here that collaboration between molecular biologists and epidemiologists offers a new and potentially fruitful approach.

Table IV. Cancers weakly associated with smoking

Association causal	**Association partly causal, partly due to confounding**
Cancer of	
lip	Cancer of liver[a]
nose	
nasopharynx	**Association partly or wholly due to confounding**
stomach	
renal body	Cancer of large bowel
Myeloid leukaemia	Cancer of cervis, uterus

[a]Association moderately strong.

In examining the possibilities for control, I shall sometimes need to examine the trends in the incidence of different types of cancer over time. Unfortunately, national cancer incidence data are available only from 1971 to 1989 and the trends are difficult to interpret, partly because they have been influenced artificially by changes in the completeness of registration and partly because of the introduction of intensive screening. I shall, therefore, for the most part, have recourse to trends in mortality, which are available for a longer period and are less susceptible to such artefacts, although they may be influenced by improvements in treatment.

Tobacco smoke

By far the most important avoidable cause that principally requires research into how to get our knowledge of it applied is tobacco smoke. This, Peto *et al.* estimate will still be responsible for 40% of deaths from cancer in men in this country in 1995, having come down from 52% 20 years earlier, while the proportion in women will be 20%, having increased over the same period from 12% (4). When the epidemic in men was at its height, smoking was responsible not only for 95% of all lung cancers in men but also, as agreed by the IARC (5), for a large proportion of all cancers of the mouth, oro- and hypopharynx, larynx, oesophagus, pancreas, bladder and renal pelvis; and it is now clear that it also accounts for a small proportion of most of the other cancers listed in Table IV. For the risk of all these cancers is increased in cigarette smokers and particularly in heavy smokers. For most of them the association is almost certainly causal; for one it is partly causal and partly due to confounding; for two it may be wholly due to confounding with other factors that are the primary cause (6). That smoking should be a cause of so many different types of cancer should not be surprising, as inhalation is a most effective way of distributing chemicals throughout the body and tobacco smoke contains at least 50 chemicals that are known to be carcinogenic in animal experiments, including radioactive polonium, benzene, 2-naphthylamine, 4-aminobiphenyl, and various polycyclic aromatic hydrocarbons and nitrosamines.

Sex-specific trends in the mortality from lung cancer, which closely reflect the trends in incidence, because the fatality continues to be so high, parallel the trend in the prevalence of cigarette smoking adjusted for tar yield, after appropriate allowance for latent period and cohort effects (7), but the same is not true for several of the other cancers that are caused in large part by smoking. Table V compares the changes in mortality from these cancers over the last 20 years with those

Table V. Per cent change in mortality 1970–1974 to 1990–1991: cancers closely associated with smoking

Type of cancer	% change			
	Males, aged (years)		Females, aged (years)	
	35–49	50–69	35–49	50–60
Lung	−49	−34	−21	+50
Mouth	+82	+80	+33	+37
Pharynx	+46	+12	−59	−37
Oesophagus	+36	+58	−31	+26
Larynx	−5	+7	−41	+9
Pancreas	−23	−15	−15	+3
Bladder	−47	−19	−33	−4

from lung cancer. Data are given separately for ages 35–49 years, which can have been affected only by relatively recent changes, and for 50–69 years, which are also affected by changes in the more distant past.

Clearly there have been other factors that have affected the risk of cancer of the upper digestive tract in men and cancer of the mouth in young women, one of which is likely to have been the increased consumption of alcohol and another might be increased infection with the papilloma virus, but there must also have been one or more others that have caused the reduction in mortality from cancers of the pharynx and bladder in older women.

Alcohol

There is little new to say about alcohol, except that it looks increasingly likely that even quite small amounts do cause some increase in the risk of breast cancer in women, possibly by interfering with the metabolism of oestrogens, as well as the established risk of oropharyngeal, oesophageal, laryngeal and hepatic cancers. There is, however, little possibility of reducing the risk of cancer by reducing its consumption, except in so far as education, taxation and medical intervention can reduce the prevalence of such heavy consumption that it causes cirrhosis of the liver and, secondarily, hepatic cancer. This is because we now know that consumption of moderate amounts, say an average of 2–4 units a day, reduces the incidence of ischaemic heart disease by some 40%. In countries where the risk of ischaemic heart disease is high, as in the UK, policies aimed at a drastic reduction in the consumption of alcohol might, at least in terms of mortality in middle and old age, do more harm than good. From the point of view of preventing cancer among non-smokers, the avoidance of alcohol is of little importance, as alcohol and tobacco act synergistically and the risks attributable to alcohol in non-smokers are small. Hence, the great majority of the cancers caused by alcohol can be avoided by avoiding smoking.

Infection

The prevention or treatment of infection offers some of the most promising methods for the control of cancer, ranging from hygienic measures to prevent the spread of parasites, through chemotherapy for bacterial infection, to immunization against viruses.

Parasitic infection need not concern us directly in the UK, as parasites that contribute to the causation of many bladder cancers, colorectal cancers, and hepatomas and cholangiocarcinomas in parts of Africa and Asia are not found in Britain. Where they do occur they could be eliminated by measures to eliminate the relevant schistosomes and liver flukes, given sufficient public collaboration.

A preventive measure that must be worth considering here, and much more so in countries where gastric cancer is common, is medical treatment to eliminate infection with *Helicobacter pylori*. Infection of the gastric mucosa commonly occurs in youth and causes antral gastritis, which leads to duodenal ulcers and (less specifically) to gastric ulcers. Eventually it leads to atrophic gastritis and intestinal metaplasia. These in turn lead to gastric carcinoma, which has consistently been found to be associated with *Helicobacter* infection in both case-control and cohort studies. Antibiotic treatment can eliminate the infection and is an effective treatment for duodenal ulcer, but whether it would materially reduce the risk of gastric carcinoma remains to be shown. *Helicobacter pylori* is, however, certainly a cause of gastric lymphomas, for the presence of lymphoid follicles is a characteristic feature of *Helicobacter* gastritis and infection is present in >90% of cases (8). Elimination of the infection, moreover, has caused the lymphomas to regress and possibly even to disappear (9).

Other forms of bacterial infection have not been shown to contribute much to the development of cancer, except, perhaps, in the intestine, where the bacterial flora assist digestion, and in the bladder, where chronic infection may be accompanied by the formation of carcinogenic nitrosamines. But the control of such urinary infection would have only little effect on the total incidence of the disease.

Viral infection, in contrast, has been thought to be a major cause of avoidable cancer and at one time during Nixon's presidency the NCI's main research programme was focused on the discovery of the virus that was postulated to cause cancers of all types, with the object of finding a means to immunize against it. Now, however, it is clear that different viruses are responsible for different types of cancer and that many viruses may be involved. Immunization against the hepatitis B virus (HBV) is the only type of immunization against cancer now in use. In some parts of Africa and Asia, where hepatocellular carcinoma attributable to HBV infection is common, immunization should make a major contribution to cancer control, but it will have little impact in the UK, except in a few groups at special risk. What could be important in the UK would be a vaccine against the carcinogenic types of the human papilloma virus, which might virtually eliminate cancers of the cervix, vulva and vagina, and possibly cancers of the penis and anus, and might also reduce the risk of cancers of the mouth, larynx and skin. Immunization with gene segments of specific papilloma types has been shown to be effective in animals and it may not be long before a vaccine against some of them is tested in humans.

Other cancers potentially avoidable in the same way (Burkitt's lymphoma, some other lymphomas, and nasopharyngeal carcinomas attributable to the Epstein–Barr virus, the adult T cell lymphoma-leukaemia syndrome, and Kaposi's sarcoma) are uncommon in the UK, but their frequency elsewhere justifies research into the preparation of vaccines against them. A vaccine effective against the EB virus in susceptible species of monkey has been prepared, but not, to my knowledge, tested in humans. How infection with the RNA virus, hepatitis C, which is also a cause of liver cancer, can be avoided is less easy to see.

Electromagnetic radiation

Exposure to electromagnetic radiation may offer almost as many possibilities for beneficial control, including as it does

exposure to ionizing radiation, UV light, and the fields from lower frequency sources ranging from radiofrequency to the extremely low frequency fields produced by the passage of electric current.

Ionizing radiation. Ionizing radiation is estimated to cause ~4% of all cancers, mostly as a result of natural radiation to which everyone is exposed from the radon in the air, cosmic rays from outer space, external radiation from the radionuclides in rocks, soils and building materials, and internal radiation from the naturally radioactive traces of potassium, lead and polonium in food. Of this natural radiation only some of that from radon, which in the UK provides a little over half the total dose, can be avoided. The radon concentration indoors varies 100-fold throughout the country and, where it is high, the dose can be reduced by ventilation or, in the future, by building regulations that prevent most of it entering homes. Precisely how much lung cancer in the general population is caused by radon is still a matter for debate, as the effect has to be extrapolated from observations on heavily exposed miners. It will probably not be more than ~6%, but action to reduce the risk is certainly advisable for the relatively few people who are very heavily exposed. Some further reduction in exposure to medical uses of radiation, which now accounts for 97% of the exposure from man-made sources and 14% of the total exposure, is doubtless possible, but the total benefit to be gained is very small, especially as much of the medical exposure is of people who are already near the end of their lives.

UV light. More benefit could be expected from a reduction in exposure of the skin to sunlight; for sunlight, and presumably the UV component, is responsible for nearly all melanomas and basal cell carcinomas of the skin and, now that occupational exposure to coal tar and pitch has been effectively eliminated, for nearly all squamous carcinomas of the skin as well. Of the three, squamous carcinoma is the most closely related to cumulative exposure, while melanoma seems to be specially related to the frequency of sunburn, particularly in youth. The incidence of melanoma has been increasing steadily in all white-skinned populations for many years. In England and Wales mortality more than doubled in men at ages 50–69 years between 1970–74 and 1991–92, and increased by 53% in women. This has been attributed to the increased exposure from changes in clothing, exposure of the skin and travel to hot countries. The obvious way to avoid these cancers is to avoid prolonged and intensive exposure to sunlight, but this is socially unattractive, at least in countries like the UK where a tan is regarded as an indication of health. There has, therefore, been a tendency to emphasize the alternative use of sun-screen ointments. Now, however, there is accumulating evidence that such ointments, particularly if they contain psoralen, may actually increase the risk of the most serious type of skin cancer, namely melanoma. Several studies have now pointed in the same direction, the results of the latest of which are summarized in Table VI. It may be that all that this is telling us is that sun-screens increase risk in so far as they allow people to be exposed for longer without getting sunburn; but that would not explain the specific risk associated with the use of psoralen. More research into the effect of sun-screens is certainly needed. Meanwhile we can suggest only the avoidance of unnecessary exposure, particularly when the sun is high in the sky and exposure to UV light is maximal.

Until recently it was not thought that UV light was likely to cause any other type of cancer, but there is now evidence to suggest that it may also affect the risk of non-Hodgkin's lymphoma (NHL) and chronic lymphatic leukaemia (CLL), which may be considered as a clinical variant of NHL. Cartwright *et al.* suggested a relationship with NHL on the basis of a rather eclectic geographic correlation (10), but the possibility has to be considered seriously, especially since Adami *et al.* have found that, in the experience of the Danish and Swedish cancer registries, squamous carcinoma and melanoma of the skin, but not other cancers, are much more common than would be expected after the occurrence of NHL and CLL (11). Their findings are summarized in Table VII. If this relationship is confirmed in other studies, it might explain the steady increase in the incidence of NHL, which has followed, but has been somewhat slower than, the increase of melanoma. If the relationship with exposure to UV light is confirmed, it might possibly be explained by the effect of UV light on the immune system and it would certainly strengthen the reason for avoiding unnecessary exposure.

Radiofrequency and extremely low frequency radiation. Whether the radiation from other parts of the electromagnetic spectrum, or the individual electrical and magnetic fields produced, cause any risk of cancer is currently a subject of intensive research. Experimentally there is no reason to think that they do, or even, in the case of the extremely low frequency electric and magnetic fields, that they produce any biological effect that could be related to cancer, though claims of such effects have been made by individual investigators, as yet unconfirmed in other laboratories. Nor is there any epidemiological evidence of cancer production from the use of cellular telephones, the claim for the production of brain cancer being based on the occurrence of single cases.

There is, however, some good quality epidemiological evidence that residence near high-power electricity cables

Table VI. Risk of skin melanoma by skin type and sun-screen use

Sun-screen use	Odds ratio[a] for skin phenotype	
	I–II	III–IV
Never (142, 197)[b]	1.0	1.8
Ever, standard type only (230, 210)	1.8	2.2
Ever, psoralen sunscreen (43, 26)	2.1	9.8

[a]All raised odds ratios $P < 0.05$.
[b]Number of cases and controls in parentheses.

Table VII. Relationship between risks of skin cancer and non-Hodgkin's lymphoma and chronic lymphatic leukaemia (after Adami *et al.*, 11)

Following	Relative risk of developing			
	Non-Hodgkin's lymphoma	Chronic lymphatic leukaemia	Squamous carcinoma of skin	Melanoma of skin
Non-Hodgkin's lymphoma	–	–	5.5 (4.6)[a]	2.4 (1.8)
Chronic lymphatic leukaemia	–	–	8.6 (7.2)	3.1 (2.1)
Squamous carcinoma of skin	2.0 (1.7)	2.4 (1.9)	–	–
Melanoma of skin	1.4 (1.1)	0.9 (1.6)	–	–

[a]Lower 95% confidence limit except chronic lymphatic leukaemia after melanoma of skin (upper limit).

producing magnetic fields in houses of the order of 0.2 μT and above (the average in houses in this country being of the order of 0.05 μT) may approximately double the risk of childhood leukaemia and perhaps also cause a somewhat smaller increase in childhood brain cancer, and there is some evidence that occupational exposure to similar levels may increase the risk of leukaemia and brain cancer in adults. The numbers of cases in the best studies are small, but we must, I think, conclude that the possibility of a risk from such exposures exists, and that we urgently need research to determine whether it does exist or not. The fields concerned are almost wholly man-made and, if the risk is real, there will certainly be an opportunity of reducing them, though at considerable social cost.

Diet

Diet as a means of controlling cancer has, I suspect, received more attention than any of the other factors discussed, but firm evidence of its value is sparse and little new evidence has been obtained in the last 10 years. Five relationships have, however, been established sufficiently clearly to justify intervention to reduce the risk of one or other types of the disease.

First, dietary restriction reduces tumour incidence and fertility and increases lifespan in rodents compared to *ad libitum* feeding, possibly for the evolutionary benefit of maintaining the individual through periods when food is scarce to reproduce when resources improve (12). In humans, restriction in youth leads to failure to achieve full growth, delays sexual maturity in both sexes, and decreases the subsequent risk of breast cancer, testis cancer and a few other specific cancers (13). It is not a practicable means for controlling the disease, but the avoidance of obesity is and could reduce the risk of three cancers associated with obesity, namely breast cancer after the menopause and cancers of the endometrium and gall-bladder.

Secondly, salted and salt preserved food has been consistently associated with cancer of the stomach. People who consume relatively large amounts have been found to have an increased risk of ~80% in comparison with those who consume little in case-control studies in China, France, Italy, Japan, the UK and the USA (14), but whether this is due to the salt or to microbiological contamination is unclear.

Thirdly, a special type of salted fish has been so closely associated with the development of nasopharyngeal carcinoma in Southern China, especially when eaten in childhood, that it is accepted as a cause of the disease in conjunction with infection with the EB virus.

Fourthly, aflatoxin, a carcinogenic metabolite of the fungus *Aspergillus flavus*, which may contaminate stored oily foods in hot climates, is similarly associated with the risk of liver cancer in high-risk areas and has been accepted as a cause of the disease in conjunction with infection with the hepatitis B virus.

Fifthly, a high consumption of fruit and green and yellow vegetables has consistently been found to be associated with a low incidence of many types of cancer, since Hirayama drew attention to the relationship in his cohort study of 270 000 Japanese in 1979 (15)—a relationship that had been reported by Stocks and Kahn in a case-control study in 1935 and totally ignored (16). Now the evidence is overwhelming. Reviews of nearly 200 studies have consistently associated the incidence of many different types of cancer with a low consumption of fruit and vegetables. The quarter of the population with the lowest intake compared to the quarter with the highest has had approximately double the incidence of cancers of the oral cavity, oesophagus, stomach, pancreas, colon, rectrum, lung, larynx, breast, cervix, ovary and bladder (17–19). Differences between the associations with the different types of cancer have been small, except that the association with lack of fruit has been particularly marked for cancer of the stomach (14) and the association with cancer of the breast has been less marked, the excess with low consumption being only about a third.

The effects produced by the other main categories of food are less clear, possibly because of the difficulty in quantifying the components of diet over a long period and the small range of variation within most developed countries. Evidence for a specific effect of fat on the risks of breast, colorectal and prostate cancers, which are clearly correlated with national figures for fat consumption, is conflicting. However, there is agreement in epidemiological studies that if fat has a deleterious effect it is only the saturated component that is harmful. Red meat has been specifically associated with the risk of colorectal and prostate cancers and fibre negatively with the risk of colorectal cancer, but in each case the evidence is weak and it is difficult to see how firm conclusions are going to be reached in the absence of large-scale controlled trials. One small controlled study of patients with skin cancer reported a reduction in recurrence with a diet that reduced the contribution of fat to a constant total of calories from 38 to 21% (20), but studies large enough to provide a conclusive result are exceptionally difficult to carry out and have not yet been achieved. Firmer evidence about the effect of fibre may, however, be obtained from observational studies now it is realized that some starches are resistant to digestion in the small bowel and contribute to the amount of foodstuff reaching the large bowel that can serve as pabulum for bacteria, the mass of which in large bowel may protect against the development of large bowel disease.

What the specific chemicals in food are that cause or protect against cancer are still unclear (apart from aflatoxin, referred to previously). Several components of food might act as antioxidants but it is difficult to disentangle their effects in observational studies. One possibility of doing so is by experiment, which, in this case, is practicable as supplements are both easy to administer and mostly harmless, at least in the doses likely to be required. Experience of the few controlled trials to date has, however, been disappointing. In China, a supplement of β-carotene, selenium and vitamin E was associated with a decreased risk of gastric cancer (21), but in the USA vitamins C and E and β-carotene failed to reduce the recurrence rate of colorectal polyps, and β-carotene failed to reduce the recurrence of cancers of the skin (22,23). In a large controlled trial in Finland, vitamin E was unrelated to the risk of lung cancer, while β-carotene was associated with a marginally significant increase in risk (24). The duration of these trials may have been too short for benefits to be seen, but it is discouraging that the controlled trial in American doctors (25) has already continued for >12 years, without the data monitoring committee seeing the need to report the results.

Other chemicals that have been considered include vitamin A, which regulates cell differentiation *in vitro* and reduces tumour incidence in many animal experiments. However, the amount of vitamin A in serum has not been associated with the incidence of cancer in cohort studies in which serum banks have enabled vitamin concentrations to be measured well

Table VIII. Chemicals in food that might affect the risk of cancer

Chemical	Action
Natural	
Folate	reduce risk
Indoles	reduce risk
Plant oestrogens	reduce risk
Vitamin D	reduce risk
Plant carcinogens	trivial
Products of cooking	
Nitrosamines	increase risk
Heterocyclic amines	increase risk
Furans	increase risk
Polycyclic aromatic hydrocarbons	increase risk

before the disease arose. Some other chemicals are listed in Table VIII. Folic acid is required for the synthesis of DNA nucleotides and influences DNA metabolism, and a low intake of folates causes chromosome breaks. Indoles, principally found in Brassica, induce detoxifying enzymes. Weak oestrogens found in many plant foods may compete with endogenous hormones by combining with oestrogen receptor sites and act as anti-oestrogens, and vitamin D, for which receptors exist in normal large bowel epithelium, inhibits the growth of colonic cancer cells (26). None of the carcinogens that occur naturally in many fruits and vegetables is, I think, present in large enough amounts to be taken seriously on present knowledge as a potential cause of disease.

Last is the effect of the preparation of food, as cooking or smoking may lead to the production of chemicals that can cause cancer in rodents. These include nitrosamines, heterocyclic amines, furans and polycyclic aromatic hydrocarbons. Some weak association has been observed between smoked food and gastric cancer, but the IARC was unable to find any human evidence of a harmful effect of cooking food (27).

At present, the only clear ways in which the risk of cancer can be reduced by dietary means in the UK is by restricting consumption to avoid obesity and by increasing the consumption of fruit and green and yellow vegetables. A practicable recommendation for the latter, according to both the US National Cancer Institute and the Department of Health, is to consume at least five servings a day. To that I would personally add a reduction in saturated fat and red meat and an increase in dietary fibre and resistant starch, but although it would reduce blood cholesterol (and hence heart disease) the contribution that that would make to a reduction in the risk of cancer is unproved.

Physical activity

With diet we must also consider physical activity, for reduced activity seems to be as important a cause of obesity as overconsumption. Indeed it is otherwise difficult to explain the increasing prevalence of obesity in this country coupled with a decline in national consumption (28). Apart from this nonspecific effect there is also some evidence to suggest a specific effect of inactivity on the risk of cancer of the large bowel.

Reproduction

Natural sex hormones, rather surprisingly, may be some of the most important determinants of the risk of cancer, notably of cancers of the reproductive organs, but possibly also colorectal cancer. Such hormones might be expected to act primarily by causing cell division, which inevitably involves a risk of mutation, but they may also act in other ways. That they can affect the risk of some types of cancer is clear, because of the way the risks of cancers of the female reproductive organs are affected by age at menarche, age at menopause, parity, pregnancy, age at delivery, and lactation, and likewise the risk of cancer of the testis in males is affected by age at sexual maturity. Intervention to affect these factors is, however, socially unacceptable, except to encourage lactation, as breast feeding may be desirable for other reasons. The avoidance of cancer by modifying the secretion of natural hormones may, therefore, be difficult unless it can be achieved in ways unrelated to reproduction, as, for example, by diet (which has been discussed above) or by the prescription of hormonal preparations or other drugs that have similar effects (some of which are discussed below).

Medicines and medical procedures

Avoidance of particular medicines and medical procedures now offers few possibilities that have not already been exploited, except perhaps for the control of steroid contraceptives and hormone replacement therapy, but the use of some drugs may be beneficial, including some hormone preparations and the new wonder drug, aspirin.

Steroid contraceptives have been accused of having many harmful effects in the past, most of which have been reduced by reducing the dose. Their efects on the risk of cancer have remained controversial, but now, with the massive amount of data that has been collected, it seems clear that an increased risk of breast cancer affects only women under ~45 years of age when a 50% increase over the normal risk is still small, and that this is compensated for by a probable decrease in the risk of endometrial cancer and a definite decrease in the risk of ovarian cancer later in life.

Hormone replacement therapy, when limited to the use of oestrogen, certainly increases the risk of endometrial cancer and probably causes some small increase in breast cancer, as the combined preparations may also do. The benefits have, however, yet to be adequately quantified, including a possible reduction in the risk of large bowel cancer as well as a reduction in osteoporosis and ischaemic heart disease. A reduction in large bowel cancer was not suspected until the last few years, when reductions in risk began to be reported in large cohort studies. Conflicting results have been reported in a few case-control studies, but three large cohort studies report reductions of 18%, 20%, and 48% respectively in current users (29–31). The largest also reports a reduction in ex-users (27%) and an increasing reduction with duration of use (31). Two mechanisms are possible: a reduction in the concentration of bile acids in the colon; and a direct effect on the growth of cells, as oestrogen receptors occur in both colorectal carcinomas and normal colonic mucosa. It seems, therefore, that even in the interests of controlling cancer, no action need be taken to discourage hormone replacement use, which may have additional benefit in a reduction of osteoporosis and heart disease.

Medicinal treatment aimed at reducing the risk of cancer is a new concept, but there are already several possibilities. Tamoxifen, which mimics oestrogen in some respects, but also acts as an anti-oestrogen by blocking oestrogen receptors, reduces the risk of developing a new cancer in the second breast when given for the treatment of cancer in one, and controlled trials are now under way to see whether its use will reduce the risk of breast cancer in women who are at above average risk of developing the disease. More ambitiously, Henderson *et al.* have proposed the use of a modified oral contraceptive that will mimic the effect of an early menopause

and perhaps cut the risk of breast cancer in half (32); however, the preparation has yet to be tested.

Aspirin is a drug whose use as a prophylactic against cancer would, I suspect, have been thought absurd until recently, but there is now evidence from six studies that its use may approximately halve the risk of colorectal neoplasms (adenomas and carcinomas alike) and there is contradictory evidence from only one (see 33 for references). There is, moreover, experimental evidence that Sulindac (a similar non-steroidal anti-inflammatory drug) can decrease the number of polyps in patients with familial adenomatous polyposis (34). Sulindac has been shown to protect against chemically induced colonic tumours in animals and presumably acts like aspirin by blocking the production of prostaglandins, which among other things can inhibit progression from the G_1 to the S phase of the cell cycle *in vitro*.

Occupation and pollution

Two categories of cause remain for which I see little possibility of material benefit from their further control, namely the hazards of occupation and pollution. Occupational hazards, particularly coal tar fumes, asbestos and aromatic amines, have caused many cases in the past but the hazards that have been known about for years are now strictly controlled, at least in Britain, and no new ones have been discovered in the last decade.

Pollution, which is popularly thought to be a major hazard, must cause some cases, but the risks that can be quantified—those of polycyclic aromatic hydrocarbons, trace metals and benzene from the use and combustion of fossil fuels in industry and transport, dioxins from the combustion of waste, pesticide residues in food and discharges from the nuclear industry—all appear to be so minute that the social cost of trying to reduce them further may well outweigh any benefit from reduction in the incidence of cancer. One possible exception is the pollution of drinking water with trihalomethanes caused by the action of chlorine on organic waste. From an overview of 10 studies in the US, Morris *et al.* estimated that 8% of rectal cancers and 15% of bladder cancers in the US were attributable to chlorinated by-products in the drinking water (35). The evidence is not compelling, but does point to a need for further study.

Concluding note

In this review I have tried to distinguish the areas where the possibilities for the avoidance of cancer rest primarily with the application of existing knowledge and those where the new opportunities for research are most urgently needed. For both purposes it is important to know which cancers are escaping from control and becoming progressively more common. I conclude, therefore, by drawing attention to eight that have become substantially more common in youth and middle age in the last 25 years and have continued to do so in the latest available data. For five that have been largely unaffected by changes in treatment I have used mortality data; for three that have been substantially affected I have used incidence data. The findings are summarized in Table IX.

I have noted previously that the increase in mortality from cancers of the mouth and oesophagus in men may be attributed to the increase in consumption of alcohol, but the increase is surprisingly large when the reduction in smoking is allowed for, and it might be wise to look for viral infection and other factors. The increase in cancer of the pleura, which according to Peto *et al.*'s analysis must be expected to continue for another 20 years (36), can be attributed to past exposure to amphibole asbestos, principally in the building industry. The increase in mortality from cancers of the kidney in women can hardly be explained by the increase in cigarette smoking, as the mortality from both lung and bladder cancer in women under age 50 has decreased, and some other factor needs to be sought, as it does for cancer of the prostate in men, the causes of which are still essentially unknown.

Table IX. Cancers that have become substantially more common in England and Wales: percentage increase since 1970–1974

Type of cancer	Sex	% increase in age-standardized rate since 1970–1974		
		Mortality 1990–1991: aged (years)		
		35–49		50–69
Mouth	M	82		80
Oesophagus	M	36		58
Pleura	M	153		260
Kidney	F	47		38
Prostate	M	38		51
		Incidence 1988–89: aged (years)		
		15–34	35–49	50–69
Melanoma	M	84	115	142
Melanoma	F	88	99	110
Testis	M	43	43	18
Non-Hodgkin's lymphoma	M	14	66	84
Non-Hodgkin's lymphoma	F	20	81	84

I also noted previously the increase in melanoma of the skin and attributed it to greater exposure to sunlight and particularly to sunburn in youth, and have drawn attention to the suggestion that non-Hodgkin's lymphoma might be attributed to similar exposure, but the cumulative exposure rather than acute exposure causing burn. Some of the increase is an artefact associated with changing criteria for distinguishing between Hodgkin's and non-Hodgkin's lymphomas, but some is certainly real. Suggestions have also been made that the real increase might be due to increased exposure to pesticides, but the evidence to suggest such an association is weak. Lastly, there is the unexplained increase in the incidence of testis cancer, which has been going on since the First World War (as judged by mortality in the early years), has been marked in Denmark since the 1940s, and began to appear in the US only in the 1970's.

There is clearly much that could be done to reduce the risk of cancer by the application of existing knowledge, but there is equally a great deal more that has to be learnt about the causes of cancer in humans if the age-specific risk is to be greatly decreased. The collaboration of molecular biologists with epidemiologists offers a promising way of obtaining the requisite knowledge in the shortest time.

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