Papers and Originals

Cancer: The Possibilities*

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Brit. med. J., 1965, 1, 471–473

Not so long ago cancer was regarded as an inevitable accompaniment of ageing. If it was diagnosed early enough it might perhaps be treated, but few people entertained the idea that it could be avoided or that measures for cancer prevention would ever come to be an important part of public health. Now the position has altered dramatically. There is still room for a cautious optimism about the possibilities for treatment—particularly perhaps in the fields of chemotherapy and immunology—but the brightest prospects are undoubtedly for prevention. That this should be so is due to four developments.

Incidence Varies from Place to Place and Time to Time

First, we have come to realize that all the common cancers vary in incidence with changes in the environment and in the pattern of human behaviour, and that this variation may be substantial. Even within such a homogeneous area as North-west Europe and North America there is a fourfold variation in the incidence of many of the common cancers (Fig. 1), and differences between other communities are very much greater. Admittedly we do not yet know the reasons for all this variation. For example, we do not know why cancer of the stomach should be less than half as common in the white population of the U.S.A. as in England and Wales or only a third as common in the professional classes as in unskilled labourers, nor why its incidence should have fallen by a quarter in the U.S.A. in less than 10 years. Differences of this sort clearly cannot be due either to different diagnostic standards or to genetic factors, and it is reasonable to conclude that we can live a fairly full and sophisticated life without necessarily exposing ourselves heavily to the factors which cause the disease. We do, however, know some of the reasons for variation, and if we were so minded we could already reduce the British incidence of cancer of the lung to the Norwegian level.

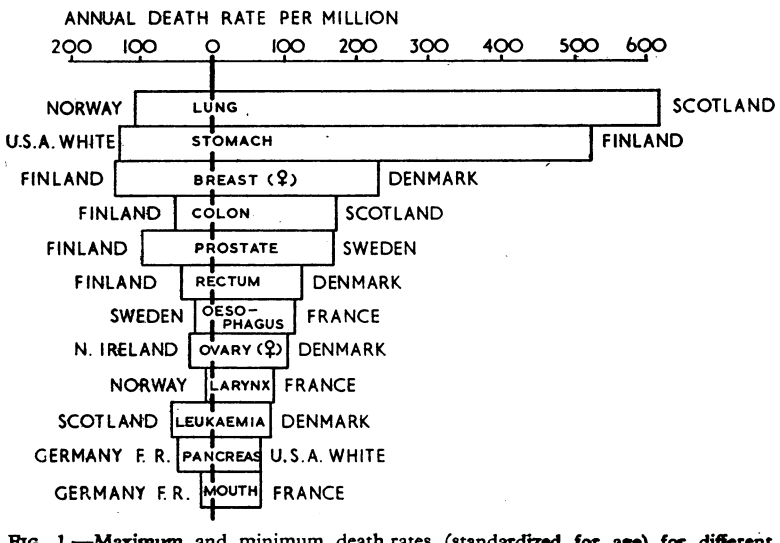

FIG. 1.—Maximum and minimum death rates (standardized for age) for different types of cancer in North-west Europe and North America, 1958–9. (Male rates unless specified female.)

Pre-carcinomatous Histological Changes

The second major development is the realization that cancer does not normally occur *de novo* in an otherwise normal tissue, but that it is usually the end-result of a process which develops over a long period and which may occur in scattered foci throughout the organ. Moreover, it seems probable that this process may be interrupted before clinical cancer ever appears. Cancers of the cervix uteri, for example, are preceded by lesions which show no evidence of invasion, but in which the individual cells have many of the characteristics of malignancy. These lesions may persist for ten years or more before showing signs of progression, or they may apparently regress. They are, moreover, in all probability preceded by an earlier stage characterized by the appearance of single cells, or small groups of cells, with abnormal nuclei.

Similar histological findings have been observed in the bronchi, stomach, oesophagus, and breast, and in these organs the lesions are commonly multiple. Perhaps the most striking are those reported by Auerbach, Stout, Hammond, and Garfinkel (1961, 1962). They took approximately 50 sections at necropsy from selected parts of the bronchi in over 750 subjects. In their first study, lesions comparable to those found in the cervix uteri were found in the bronchi of smokers, more often in men who had smoked heavily than in men who had smoked lightly, and most often in men who had a frank carcinoma in some other part of the bronchial tree. In their second study, in which the subjects were paired for sex, age, place of residence, and occupation, and in which the sections were examined in random order without knowing where they came from, they found that the lesions disappeared within 5 to 10 years of stopping smoking and that unusual degenerative cells were found in their place (Table I). The observation that the lesions disappear so quickly after stopping smoking would not have been unexpected a few years ago, but it accords well with the observations that have been made on the change in incidence of cancer of the lung among doctors (Doll and Hill, 1964).

The realization that these lesions exist is, of course, of little practical value unless it is possible to diagnose them during life and to treat them. And this presents a different problem for each type of cancer. For

* Read in opening a Symposium on Cancer at the Annual Meeting of the British Medical Association, Manchester, 1964.

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TABLE I.—*Histological Changes in the Bronchial Mucosa in Relation to Smoking Habits (After Auerbach et al., 1962)*

Subjects	No. of Subjects	No. of Sections	Percentage of Sections Showing		
			Epithelial Lesions	Atypical Cells	Carcinoma-in-situ
Non-smokers	72	3,537	26	1	0
Cigarette smokers: Continuing	72	3,156	98	93	8
Cigarette smokers: Ex-	72	3,436	67	6	1
Cigarette smokers: "Young"	59	2,851	98	97	2
Cigarette smokers: "Old"	59	2,675	98	95	12
Cigarette smokers: 2 packs or more a day	9	—	100	—	21

diagnosis the most promising method is the cytological examination of smears obtained from the affected epithelium. This method was applied by Papanicolaou to the diagnosis of premalignant lesions of the cervix uteri more than 20 years ago and it has now been used extensively in Canada, Norway, and the U.S.A. How radically it is necessary to treat the lesion, once a positive diagnosis has been made, is not yet established ; but it seems likely that a conservative operation, limited to a resection of the cervical epithelium up to the internal os, and allowing the possibility of future pregnancy, is adequate in the great majority of cases. These methods, when made generally available, may enable us to prevent the 2,800 deaths which this disease still causes in Britain each year. Their application should, however, still be regarded as a more suitable subject for research than for routine adoption. Several outstanding problems remain. It is, for example, not known how often it is necessary to examine a woman to be reasonably sure of picking up all new lesions before they develop into frank carcinoma. Moreover, some cancers may develop explosively without going through a prolonged premalignant stage, and it is possible that these are the ones that have led to death in the past. Whether this is so can be shown only by a large-scale attempt to prevent the disease by repeated examinations of a limited population. This was begun some years ago in British Columbia, and it already looks as if it is possible to reduce the numbers of new cases of cervix cancer that occur each year (Bryans, Boyes, and Fidler, 1964). No effect has as yet been demonstrated on the number of deaths, but this may be because the duration of the experiment has not yet been sufficiently long (Table II).

TABLE II.—*Incidence and Mortality Rates for Cancer of the Cervix Uteri in British Columbia,* 1955–62*

Year	No. of Women Examined	Clinically Invasive Cancer		Death Rate/100,000	
		No. of Cases	Incidence/ 100,000†	Crude	Standardized
1955	11,707	120	28·4	8·3	8·5
1956	15,106	119	27·2	7·7	7·8
1957	18,719	120	26·0	6·5	6·5
1958	29,875	112	23·7	8·7	8·9
1959	38,833	108	22·6	8·5	8·8
1960	58,109	96	19·7	6·4	6·6
1961	81,604	115	23·2	—	—
1962	106,173	75	15·2	—	—

* From Bryans, Boyes, and Fidler (1964) and Office of Vital Statistics, Vancouver, B.C.
† Women aged 20 years and over.

An alternative method, which still has to prove its practical value, is suggested by Bonham and Gibbs's (1962) finding that patients with cancer or a premalignant condition of the cervix show an abnormal amount of 6-phosphogluconate dehydrogenase in their vaginal secretions. Unfortunately, a substantial proportion of normal women also give positive results, but despite this the method may still represent an important advance. Not only is the cost of the test small, but the collection of the specimen is simple and the estimation can be made automatically. Even if this test fails to fulfil its original promise it is not, I think, unrealistic to suppose that it will be replaced by another and more efficient one. Nor is it unreasonable to suppose that it will be possible to extend enzyme studies to the detection of premalignant conditions in other sites.

Few other organs are so accessible to preventive surgery as the cervix uteri, but with other organs it may be possible to apply prophylactic measures that will lead to regression of the premalignant condition. It is one thing to tell a man who smokes 30 cigarettes a day that he has one chance in seven of developing cancer of the bronchus unless he changes his habits. It would be quite another matter if we could test his sputum and, if the result was positive, tell him that his chance was, say, one in three of developing the disease in the next five years.

Recognition of Those Prone to Develop Cancer

The third development provides another approach to this same problem—namely, the recognition of the subject who is particularly liable to develop the disease. For a long time it has been realized that the extent to which an individual is exposed to a carcinogen is only one aspect of aetiology. With a sufficiently intense exposure, as, for example, was suffered by the small group of men who were wholly employed on the distillation of β-naphthylamine, 100% may be affected ; but in less extreme conditions the proportion is usually relatively small. Even among the 2,500 residents who survived the explosion of the atomic bombs at Hiroshima and Nagasaki and who were within 1,100 metres of the hypocentre, the proportion who have developed leukaemia is less than 2% (Brill, Tomonaga, and Heyssel, 1962). This is many times the expected proportion, and even this figure reflects an important leukaemogenic effect of radiation ; but why were these 2% affected and the others not ? It is possible to explain this selection solely on statistical grounds—by postulating that everyone is equally susceptible to the disease, but that its induction depends on the occurrence of one or more events that are unlikely to be produced in exactly the right way even in the presence of a large dose of the exciting agent—and this may indeed be the usual explanation. Recently, however, there have been encouraging signs to suggest that variations in individual susceptibility may play a part, and that these may be capable of detection.

In a few rare instances genetic factors are of overwhelming importance, as in polyposis coli, which is determined by a single dominant gene and which leads almost invariably to cancer of the large bowel. At the other end of the spectrum the effect may be slight, as with the gene which determines the possession of the blood-group A substance and which increases the suceptibility to gastric cancer by about 20%. In this case, however, it is possible that the blood-group gene is only one of a group of interacting genes including, for example, the gene for secretor status. The total effect of such a group on susceptibility might be considerable, but their interaction would be difficult to detect in family studies. Evidence has been put forward to suggest that genetic factors, all of which are potentially capable of recognition, may also play some part in determining susceptibility to several other cancers, including leukaemia (Barber and Spiers, 1964), cancer of the lung (Tokuhata and Lilienfeld, 1963a, 1963b), and cancer of the breast (Penrose, Mackenzie, and Karn, 1948). It must be admitted, however, that evidence from unbiased twin studies, which is slowly being accumulated in Denmark and Germany, makes it unlikely that genetic factors will prove to be of major importance in determining differences in susceptibility for the majority of cancers (Hauge and Harvald, 1961 ; Nielsen and Clemmesen, 1957).

Other factors that may be capable of recognition include the pattern of hormone secretion. Bulbrook and Hayward and their colleagues at the Imperial Cancer Research Fund Laboratories and at Guy's Hospital have shown that women with breast cancer who excrete in the urine subnormal amounts of the androgen metabolite aetiocholanolone have a poor prognosis. Excretion is not related to the clinical stage of the disease, and the discriminatory value of subnormal excretion appears also to be of prognostic value in early cases (Bulbrook, Greenwood, and Hayward, 1960 ; Bulbrook, Hayward, Spicer, and Thomas,

1962 ; Bulbrook, Hayward, Thomas, and Atkins, 1964). If, as seems likely, the pattern of excretion is determined before the cancer develops, it may be possible to pick out a group of women who have a particularly high risk of dying of breast cancer and to treat them prophylactically before the disease has appeared—for example, by inducing an early menopause or by giving prophylactic doses of androgen.

Others have studied psychic factors, and these, according to Kissen (1964), may be of special significance in determining the incidence of cancer of the lung. That they should have a direct effect on the development of cancer is not an obviously attractive hypothesis. But it is not inconceivable that they should have an indirect effect—for example, by modifying the depth and frequency of inhaling—and their study may help to identify high-risk groups, on whom preventive measures could be concentrated.

Developments in Virology

The fourth development is, of course, the field of virology. From being an isolated curiosity virus-induced cancers have become commonplace ; more than 50 viruses capable of causing cancer under suitable conditions are known and virus-induced cancers have been observed in so many animals that it would be surprising if man was completely immune. If they do play a part in human cancer, new ways of combating the disease—by preventing transmission and by inducing immunity—are immediately suggested.

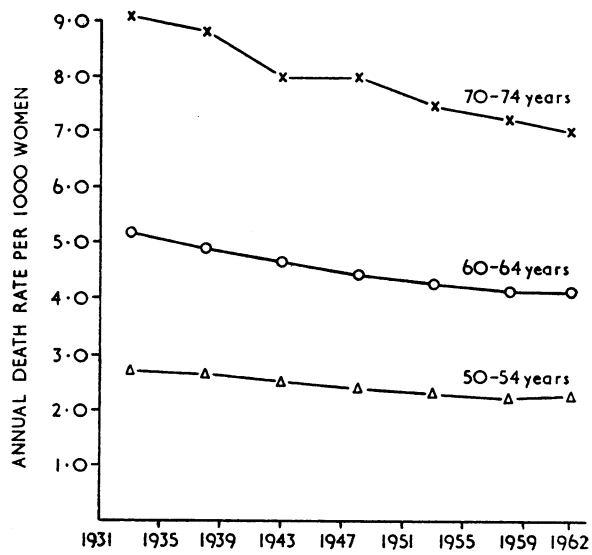

FIG. 2.—Trend in total cancer mortality among women in England and Wales, 1931–62, at different ages.

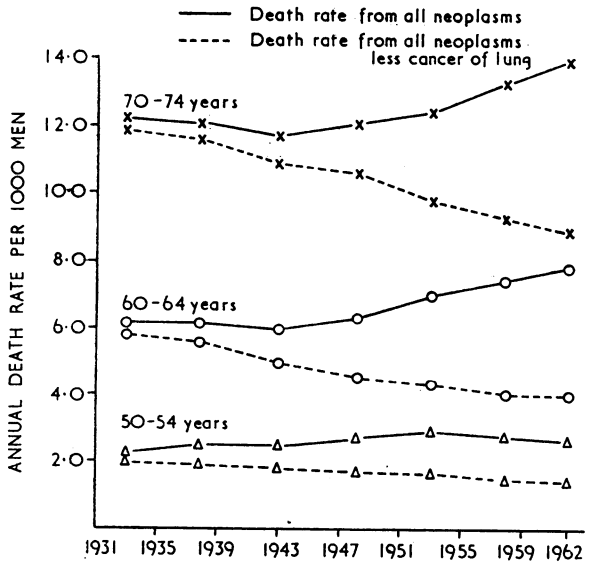

FIG. 3.—Trends in total cancer mortality, including and excluding cancer of the lung, among men in England and Wales, 1931–62, at different ages.

Conclusions

In the light of all these developments, we should, I think, be unduly pessimistic if we did not anticipate an appreciable reduction in the toll of cancer over the next decade. The proportion of deaths due to cancer will in all probability continue to rise, as other diseases are brought further under control and the proportion of old people in the population continues to increase ; but the death rate at each age can reasonably be expected to fall. Among women this has already been happening for some years (Fig. 2). Among men, on the other hand, the rates have increased, owing very largely to the phenomenal increase in cancer at one site. If cancer of the lung is omitted, a decrease in the mortality from all other types of cancer is seen to have occurred in men also (Fig. 3). The next decade should, I believe, see the decrease accelerated in both sexes.

Summary

Cancer was once regarded as an inevitable accompaniment of ageing. Now the position has altered dramatically and cancer prevention has become a major function of public health.

This change is due to four developments. First, we now know that the common cancers vary in incidence from place to place and time to time. The causes are only partly known, but experience of different countries shows that modern civilization is compatible with a relatively low incidence of nearly every type of cancer. Secondly, it is realized that cancer does not usually arise *de novo* from an otherwise normal tissue, but is preceded by the appearance of a series of histological changes proceeding through carcinoma-in-situ to invasive cancer. If detectable these changes provide an opportunity for effective treatment, or perhaps reversion of the process, by removal of the causative agent. Thirdly, knowledge of factors that affect individual susceptibility—genetic, constitutional, and psychological—is beginning to accumulate so that prophylactic efforts may possibly be concentrated where they will be most rewarding. Fourthly, there are the immense developments in virology.

Although the annual number of deaths from cancer will continue to increase because of the increasing proportion of old people in the population, we may reasonably anticipate a substantial reduction in the mortality rate from cancer at each age over the next decade.

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