

AETIOLOGY OF BREAST CANCER: A BRIEF REVIEW

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SUMMARY

Cancer of the human breast is probably a group of diseases which have different causes. Changes in hormonal status that increase breast cancer risk probably do so by 'promoting' tumour development rather than by 'initiating' it. Exogenous oestrogens seem to act as tumour promoters in this context, but there is to date no evidence that oral contraceptives, some of which contain oestrogens in low dosage, increase breast cancer risk. On the contrary, they appear to reduce the incidence of benign breast tumours. Prolactin-release is associated with increased mammary tumour incidence in rats but not in humans. There is no evidence that viruses or exposure to hair-dyes increase breast cancer risk. The fact that slight dietary restriction can dramatically reduce mammary tumour incidence in rats, suggests that dietary factors should be looked at more closely in the search for aetiological factors in man.

KEY WORDS—Human breast cancer, aetiology, carcinogenesis.

INTRODUCTION

Two factors more than any others have served to confuse and perhaps delay our understanding of the causation of breast cancer. Firstly, there is the misconception that cancer of the breast is a single disease and secondly, there is the frequent confusion between causes and effects. Broadly based epidemiological studies which assume that there is only one disease may well have failed to reveal patterns which would have suggested aetiological mechanisms for sub-varieties of breast cancer. While too much research has been based on findings in animal studies where the common forms of the disease have no counterpart in man or correspond to only one small sub-variety of the human disease, the hormonal status of women with breast cancer and the hormone-responsiveness of their cancers may be more relevant to the consequences of cancer than to its causes.

In this paper I will briefly review the present state of our knowledge with regard to the causation of breast cancer in man in the light of the two-stage concept of carcinogenesis. My main conclusion will be that at the present time we have negligible information regarding factors which initiate human breast cancer but that dietary factors, and especially over-nutrition, along with various aspects of reproductive activity are of major importance as tumour-promoters.

THEORIES OF CARCINOGENESIS

It is almost overwhelmingly fashionable to conceive that each cancer is a large clone of cells that originates from one cell which has been rendered abnormal as a result of mutation or because it has acquired the nucleic acids of an oncogenic virus. It is also widely accepted that other agents—hormones, tumour-promoting agents, co-carcinogens, immuno-suppressant drugs, etc.—may facilitate the development of a clone of cells from a single abnormal cell. Fig. 1 summarizes this fashionable view.

This concept, which is supported not only by studies on animals and mathematical modelling, but also by epidemiological data, seemingly casts hormones firmly in the role of second-stage carcinogens or tumour-promoters rather than in the role of tumour-initiators.

The fact that mammary cancers arise in animals deliberately exposed to oestrogens and not to anything else, has led some observers to regard agents such as diethylstilboestrol (DES) as complete carcinogens. However, I believe they are mistaken in doing so since I know of no evidence that oestrogens alter cellular nucleic acids and I suggest that this is an essential aspect of tumour-initiation. On the other hand, it may well be that hormones can act not only to reveal genetic defects resulting from previous exposure to initiators, but also to render tissues more susceptible to the effects

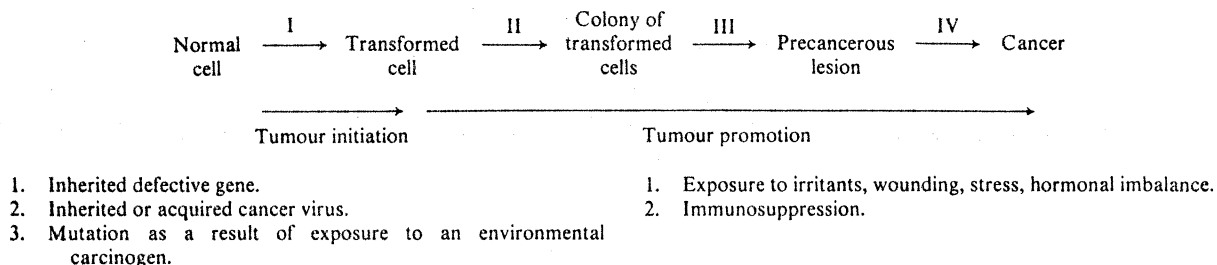


Fig. 1—Mechanism of carcinogenesis

of concurrent or subsequent exposure to initiators. This may be the reason why daughters of women given large doses of stilboestrol during pregnancy are especially prone to develop lower genital tract cancers. Exposure *in utero* to massive doses of oestrogens leads to structural changes and it may well be that the structurally abnormal tissues are hypersensitive to tumour initiators.

The following brief review of data relevant to the aetiology of mammary cancer in mice, rats and humans indicates a real dearth of information and ideas concerning possible initiators of breast cancer in man.

MAMMARY CANCER IN MICE

Overwhelming evidence from innumerable laboratory studies has shown that genetic factors, hormones and an RNA virus, transmissible in the milk, act as co-factors in the aetiology of mammary cancer in this species. The cancers which arise form a rather homogeneous group of locally invasive adenocarcinomas which rarely metastasize. The females of some inbred strains experience a close to 100 per cent incidence of mammary cancer, but this incidence can be reduced more or less to zero by fostering infants on mothers who do not secrete the virus in their milk. This picture is consistent with genetic and viral factors fulfilling the initiating stage of carcinogenesis and hormones acting as tumour promoters.

MAMMARY GLAND NEOPLASIS IN RATS

Most strains of laboratory rat are excessively prone to the development of mammary tumours. Examples of multiple mammary tumours are commonly encountered in untreated animals, but most of them are histologically benign. They range in appearance from

adenomas, though fibroadenomas, to fibromas and very often the same tumour mass includes areas of all three elements. Malignant tumours are usually adenocarcinomas, but sarcomas, usually fibrosarcomas, arise in the mammary gland region and it is difficult to be sure whether these are derived from the specialized mammary connective tissue or from ordinary connective tissue. There is no persuasive evidence for believing that an RNA virus, similar to the mouse mammary tumour virus, is implicated in the aetiology of rat mammary tumour development. On the other hand, under laboratory conditions female rats exhibit plenty of evidence of abnormal hormonal status. The incidences of chromophobe tumours of the pituitary gland, and of tumours of the adrenal cortex, adrenal medulla, thyroid and parathyroid glands, tend to be high and ovarian cysts and cystic hyperplasia of the uterus very common.

Table I illustrates the incidences of various tumours in a group of 50 untreated control female rats in a 2½ year test for carcinogenesis. I would stress that findings such as these are by no means unusual. Associated with the high incidence of mammary and pituitary tumours are high serum prolactin levels and, as we shall see, the theory has grown up from studies on rats that increased prolactin levels predispose to mammary tumour development. Irrespective of whether or not this is true for the rat, it is becoming increasingly clear that this is not so in humans.

It is interesting to speculate as to why mammary tumours and various endocrine tumours are so prevalent in laboratory rats. I suspect that enforced celibacy is partly to blame. However, by far and away the most important single factor seems to be over-feeding. Tables II and III illustrate the effects of slight dietary restriction on the incidence of mammary tumours in rats in a study carried out by TUCKER (1979) at Imperial Chemical Industries, Alderley Edge. A remarkable aspect of these findings is the fact that the restricted females ate on average the same amount of food each day as the ad libitum-fed animals. This

Table I—Tumour incidence among untreated female Sprague-Dawley rats

Time in weeks	0-60	60-80	80-100	100-120	120-123	0-123
Deaths during period	3	2	9	12	24	50
Number of rats with:						
Mammary tumours	0	1	4	8	16	29
Pituitary tumours	0	1	5	5	10	21
Other endocrine tumours	0	0	1	0	8	9
Other tumours	0	0	4	2	1	7
One or more tumours at any site	0	1	9	10	20	40
One or more malignant tumours at any site	0	0	4	1	0	5

strongly suggests that simple calorie restriction is not the most important factor. It is known that plasma cortisol levels rise in caged rats when the food basket is

Table II—Effect of dietary restriction on 'spontaneous' tumour incidence in rats (from TUCKER, 1979)

	Males		Females	
	Ad lib.	Restricted	Ad lib.	Restricted
Food consumption (g/day)	20	15*	15	15†
% survival for 2 years	72	90	68	88
% tumour-bearing animals before or at 2 years	66	24‡	82	56†
Mean number of tumours per rat	0.94	0.27‡	1.18	0.76†

* $p < 0.05$.

† $p < 0.01$.

‡ $p < 0.001$.

Table III—Effect of dietary restriction on incidence of pituitary and mammary tumours in rats (from TUCKER, 1979)

	Males		Females	
	Ad lib.	Restricted	Ad lib.	Restricted
% Rats with pituitary tumours	32	0‡	66	39†
% Rats with mammary tumours	0	0	34	6‡

† $p < 0.01$.

‡ $p < 0.001$.

removed. It seems that even an animal that is not hungry becomes anxious if it cannot see its next meal. Thus the restricted rats in TUCKER's experiment ate their limited ration as soon as it arrived and spent the rest of the 24 hours anxiously eyeing an empty food basket. However, they were amply repaid for their daily anxiety in terms of both better survival and much lower incidences of many kinds of tumour, including mammary tumours and pituitary tumours.

According to WYNDER *et al.* (1978b) high fat diets only increase mammary tumour incidence in rats exposed to DMBA if they are given *after* the DMBA. This suggests that high fat intake influences the tumour promotion stage of mammary carcinogenesis.

RISK FACTORS IN MAN

Table IV lists the main risk factors that have come to light as a result of epidemiological studies.

(i) Genetic factors

No one doubts that genetic factors play some role as determinants of breast cancer risk in humans. The

Table IV—Risk factors in humans suggested by epidemiological studies

Genetic				
Environmental				
—Geographical				
N. America	}	S. America	}	Africa
N. Europe		S. Europe		Asia
—Diet				
—Reproductive status				
Early menarche		—	↑ risk	
Late menopause		—	↑ risk	
Oöphorectomy		—	↓ risk	
Early first successful pregnancy		—	↓ risk	
(N.B. subsequent pregnancies do not increase degree of protection)				

difficulty is to ascertain whether they are important or not, or whether they apply weakly to all forms of the disease or strongly to one or two minor variants.

The fear that cancer runs in families is widespread, particularly in the case of commonly affected sites such as the breast. The discovery of the mammary cancer virus of mice has served to heighten this innate fear.

Numerous epidemiological studies have indicated a slightly increased risk of breast cancer among the female close relatives of patients with the disease. The increase is greater for cases of pre-menopausal cancer than for cases of post-menopausal cancer and markedly greater for patients with bilateral breast cancer. Exceptionally, BULBROOK (1976) concluded that a family history of breast cancer is not a risk factor for first-degree relatives.

Studies on breast cancer in twins gave results consistent with genetic factors being weak determinants. ANDERSON (1977) recorded a concordance rate of 28 per cent for monozygotic twins compared with only 12 per cent for dizygotic twins.

The importance of genetic factors is also suggested by the high incidence of breast cancer among Parsee women in the Bombay region of India. In this case it is postulated that inbreeding among this community has led to the concentration of breast cancer-prone genes and/or of an oncogenic viral pool. However, examination of the milk from such women has given no more than inconclusive evidence of an excess of RNA virus particles or reverse transcriptase enzymic activity.

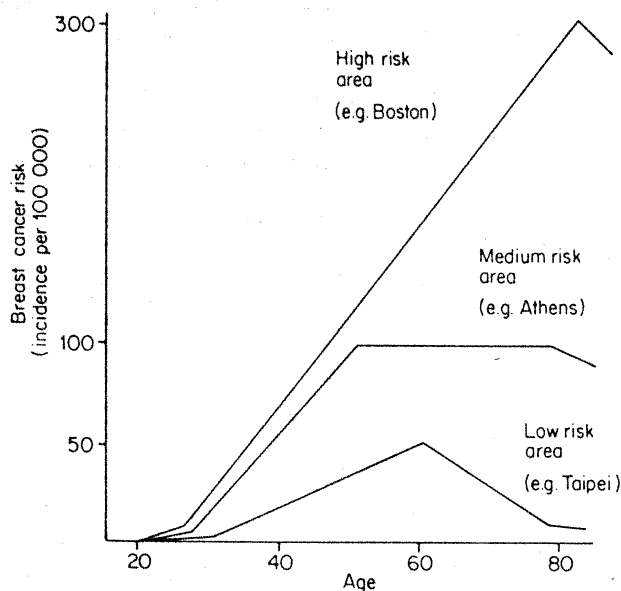


Fig. 2—Age-specific incidence rates in high, medium and low risk areas of the world. (After MACMAHON *et al.*, 1973)

(ii) Geographical influence

The life-time risk of developing breast cancer is some six-times higher in Northern Europe and North America than in most parts of Africa and Asia. Intermediate risk rates are observed in Southern Europe and South America (DOLL *et al.*, 1970). As illustrated in Fig. 2, in high-risk areas risk continues to rise after the menopause, whereas in medium risk areas it levels off and in low risk areas it falls. Following migration from low-risk to high-risk areas—as for example, migration from Japan or China to North America—breast cancer risk tends to rise during the course of 2 or 3 generations towards the level in the adopted country. This suggests that environmental rather than genetic factors are chiefly responsible for geographical differences in incidence.

The spectrum of histopathological types of tumour is basically similar in high and low-risk areas. However, MACMAHON *et al.* (1973) found higher proportions of intraductal, medullary and colloid tumours among a collection of breast cancer patients in Tokyo than among a comparable collection in Boston. Also, in the Japanese cases there tended to be a more pronounced host cellular reaction and better survival.

There is no glaringly obvious explanation for the marked geographical differences, although dietary factors and the amount of food consumed merit most suspicion.

(iii) Diet

Breast cancer tends to occur in higher incidence in rich countries than in poor ones and it seems likely that the quantity and quality of the average diet are determinants of breast cancer risk. However, social class trends are not very obvious within the high-risk rich countries of Northern Europe and North America.

Many studies have revealed correlations between obesity, overnutrition generally, and high intake of fats in particular, and breast cancer (e.g. CARROLL *et al.*, 1968; CARROLL, 1975; DE WAARD, 1969; KIM and FURTH, 1976; LEA, 1966; WYNDER *et al.*, 1978a) and many theories have stemmed from these observations. For instance, it has been suggested that dietary fat acts as a vehicle for lipid soluble carcinogens and that the seaweeds and raw fish eaten by Japanese women protect them from breast cancer. In 1971 HILL *et al.* suggested that where dietary fat is high, gut bacteria can produce steroidal oestrogens from bile acids and cholesterol. These steroids, they propose, increase breast cancer risk. However, none of these specific theories is backed up by supportive data. The fact that

Mormons, who neither smoke nor drink alcohol, have breast cancer rates similar to those for North American women generally (LYON *et al.*, 1976) suggests that neither of these environmental factors are implicated aetiologically.

It is known that obesity tends to be associated with abnormalities in sex hormone status in premenopausal women (SHERMAN and KORENMAN, 1974). However, not all authorities agree that obesity, *per se*, is an important risk factor. Obesity is, for instance, a common problem among Japanese women, although their risk of developing breast cancer is relatively low.

Personally, I suspect that overnutrition and obesity are by no means synonymous, that some aspects of overnutrition are important in the aetiology of breast cancer and that obesity is a poor index of these over-nutrition factors.

(iv) Reproductive status

Most investigators accept that there are associations between early menarche and breast cancer risk. Similarly, there is wide agreement that oöphorectomy during the reproductive phase of life reduces breast

cancer risk—the reduced risk becoming evident about 10 years after the operation. It is not clear, however, to what extent the protection offered by oöphorectomy is countered by replacement oestrogen therapy. There is also far from complete consensus of opinion concerning the relation between child-bearing and breast cancer. According to MACMAHON *et al.* (1973) in their substantial review of breast cancer aetiology, the only really important factor is the interval between the menarche and the first successful pregnancy; the shorter the interval, the lower the risk. Since the age at menarche is not all that variable, it is not surprising that there appears to be a convincing association between age at first pregnancy and risk (Fig. 3). Thus, provided that her first successful pregnancy is completed before the age of about 30, a woman has less risk of developing breast cancer at any time in her life than if she never became pregnant. However, women whose first successful pregnancy occurs after they are 30 years of age, are at higher risk of developing breast cancer sometime in their lives than are nulliparous women. Abortive first pregnancies are not protective and in some studies have been found to be associated with increased risk.

The idea that lactation protects against the development of breast cancer has always been attractive to those who intuitively believe that it is right for mothers to feed their own babies and that one is asking for trouble—such as increased breast cancer risk—if one interferes with natural processes by feeding infants artificially. However, several large studies in geographical areas of high breast cancer risk have failed to reveal any convincing evidence of protection from lactation. One study of this kind reported by KAMOI (1960) of women in Japan—a low risk area—suggested a protective effect of lactation. But subsequent studies have failed to confirm this observation.

It is interesting to speculate, as many investigators have done, as to what these various associations between reproductive status and activity and breast cancer risk mean. In general it seems fair to conclude that the longer a woman is exposed to endogenously produced oestrogens, the higher will be her risk of developing breast cancer. Thus early menarche, and late menopause, predispose and oöphorectomy protects. It is generally accepted that hormones switch genetic information on or off, but do not alter it. This casts natural oestrogens in the role of possible tumour-promoters rather than possible tumour-initiators. To explain all the facts we need to propose that in the nulliparous women, oestrogens act as potential promoters of tumour development throughout life. The hormonal disturbances of pregnancy itself might well act as a

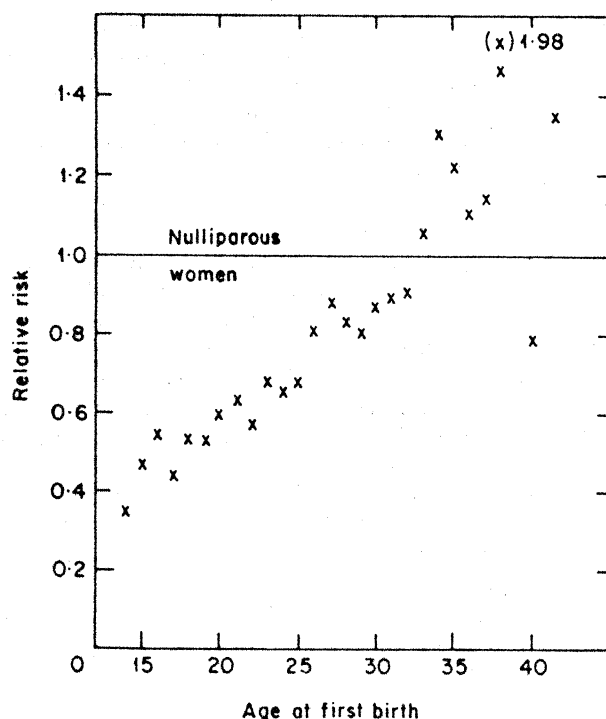


Fig. 3—Breast cancer risk according to age at birth of first child. (Relative to risk of 1.0 for nulliparous women). (From MACMAHON *et al.*, 1973)

tumour-promoting stimulus but, for some reason which is not clear, after the first successful pregnancy breast tissue becomes permanently less susceptible than before to the tumour-promoting effects of endogenous oestrogens.

This hypothesis leaves wide open the question of which factors initiate breast cancer in humans, and its plausibility relies on the concept that the human breast accumulates initiated cells or foci of cells throughout life, so that the sooner the first successful pregnancy occurs and reduces the susceptibility of the breast to tumour-promotion by oestrogens, the better.

Personally, I am doubtful of the relevance of many of the published studies on rats to the elucidation of the causation of breast cancer in humans, but the hypothesis I have just outlined is supported by observations in the rat. MOON (1969) reported that prior pregnancy decreases breast tumour yield in response to exposure to a carcinogen, whereas pregnancy after carcinogen exposure promotes tumour growth.

ARE VIRUSES IMPLICATED IN THE AETIOLOGY OF HUMAN BREAST CANCER?

Particles similar in appearance to the RNA virus particles implicated in mouse mammary carcinogenesis have been found from time to time in human milk, and so has the enzyme, reverse transcriptase. At first it was claimed that both the virus and the enzyme are more commonly present in the breast milk of women with a family history of breast cancer, than in that from women with no such family history. However, subsequent studies, such as that of SARKAR and MOORE (1972) did not bear out this claim. On the other hand, SPIEGELMAN and his colleagues (AXEL *et al.*, 1972), using nucleic acid hybridization techniques, found in human breast cancer cells, but not in cells from normal human breasts, RNA that was homologous with mouse mammary tumour virus. Such observations force one to keep an open mind concerning the possibility that viruses are implicated in the aetiology of human breast cancer. Nevertheless, we probably already know enough to be sure that even if an RNA virus is involved, it is a relatively minor determinant of the disease and in no way similar in importance to the mouse mammary tumour virus. Parenthetically, it is interesting to note that breast feeding is least common in those parts of the world where breast cancer incidence is highest, and vice versa.

ENVIRONMENTAL FACTORS WHICH MIGHT BE IMPLICATED IN BREAST AETIOLOGY

Five topics merit special consideration as possible environmental causes of breast cancer:

- (i) Exogenous oestrogens.
- (ii) Prolactin-releasing agents.
- (iii) Ionizing radiation.
- (iv) Hair dyes.
- (v) Chemicals to which women are exposed at work.

Of these the last three are potential tumour-initiators, the other two being tumour-promoters.

(i) *Exogenous oestrogens*

The fact that early menarche and late menopause are associated with increased breast cancer risk and oophorectomy is associated with decreased risk, led us to the view that endogenous oestrogen secretion serves to enhance risk. For other reasons we suspect that the enhancement takes the form of tumour-promotion rather than initiation. If these views are right and if it is true that initiated cells and foci accumulate in the breast with age, it follows that exogenous oestrogens must be regarded as potential promoters of breast cancer, especially as women get older. On the other hand since pregnancy before the age of 30 protects against breast cancer in which endogenous oestrogens may be acting as tumour-promoters, it is possible that an enhancing effect of exogenous oestrogens would be more marked in nulliparous women than in parous women (BLACK and LEIS, 1972).

As far as the contraceptive pill is concerned, the studies of VESSEY and his colleagues (1971, 1975) have not so far revealed any evidence of enhanced breast cancer risk. Both in their studies and in those of the Boston Collaborative Drug Surveillance Programme (ORY *et al.*, 1976), taking the pill was actually associated with reduced incidences of benign breast tumours, especially fibroadenomas, and of fibrocystic breast disease. On the other hand there are several well-documented case reports of breast cancer in both men and women given large doses of oestrogens for therapeutic reasons. HOOVER *et al.* (1976) reported that oestrogens given to relieve menopausal symptoms certainly do not reduce breast cancer risk and may increase it. It would be prudent, therefore, to keep an open mind with regard to possible dangers associated with the pill and, at the same time to restrict the practice of so-called hormone replacement therapy to cases of unquestionable medical need.

(ii) Prolactin-release drugs

The discovery by CHARLES HUGGINS and his colleagues of a rapid method of producing mammary tumours in rats by the oral administration of the carcinogen 7,12-dimethylbenz(a)-anthracene (DMBA) is the basis of innumerable experimental studies of breast cancer aetiology. Many studies based on the use of DMBA, or research procedures such as hypophysectomy, or the implantation of pituitary grafts, have given results consistent with the view that prolactin and agents which block the release of prolactin-inhibiting factor, favour mammary tumour development in animals previously exposed to DMBA. On the other hand, just as prior pregnancy protects against tumour development in response to DMBA, so does prolactin stimulation prior to DMBA. These laboratory studies suggest that in rats prolactin may influence the tumour-promoting phase of mammary carcinogenesis, but have no effects relevant to tumour-initiation.

Pregnancy and lactation are the only times during life when normal women are subject to significant prolactin stimulation, unless they take drugs such as reserpine, methyldopa or phenothiazines, which, in effect, stimulate prolactin release. In 1974 the results of three separate epidemiological studies reported in one issue of the *Lancet*, were considered to be consistent with the suspicion that the drug reserpine enhanced breast cancer risk. In one of these studies the enhancing effect was only seen in women over 50. The results of three subsequent studies published in the *Lancet* during 1975 failed to reveal any evidence of an association between reserpine and breast cancer risk.

WYNDER *et al.* (1978b) have suggested that high fat diets predispose to breast cancer by raising blood prolactin levels. However, this suggestion will require to be substantiated.

It is reasonable to question whether the Huggins method of rapid production of mammary tumours in rats is suitable as a model for studying the causation of breast cancer in humans. In the first place, under laboratory conditions the hormonal status of female rats is clearly far from normal. Very high spontaneous incidences of prolactin-secreting pituitary tumours and of mammary tumours would appear to render the species unsuitable for this purpose. Secondly, in many of the studies in which prolactin was incriminated as a probable cause of mammary tumour enhancement, there would have been concomitant changes in other hormones. Thirdly, as the work of MEITES and NICOLL (1966) has shown, prolactin is powerfully luteotropic in rats but this may not be so in women.

(iii) Ionizing radiation

The induction of mammary tumours in mice and rats by ionizing radiation has been repeatedly demonstrated. According to PAPAIOANNOU (1974), who reviewed the relevant literature, there are several well-documented examples of breast cancer arising in subjects exposed to ionizing radiation in therapeutic doses and a few examples in persons excessively exposed to diagnostic radiography (for example cases of pulmonary tuberculosis).

A handful of cases of breast cancer among survivors of the Hiroshima and Nagasaki atomic bombings provides additional evidence of the role of radiation. However, all in all, although the evidence is perhaps enough to caution against the excessive use of mammography as a screening procedure, it is not enough to suggest that ionizing radiation is important as a causative factor.

(iv) Hair dyes

The discovery that certain hair dye constituents are mutagenic for bacteria, has led to speculation that hairdressers and women who have their hair dyed might be at increased risk of developing one or more forms of cancer. In the case of 2,4-diaminotoluene the possibility of cancer risk is increased by the positive results of carcinogenicity tests in animals (IARC MONOGRAPH, 1978), but in the case of other hair dye ingredients the results of animal carcinogenicity tests have been equivocal.

The latest Registrar General's Occupation Morality Supplement revealed no excessive age-standardized risk of breast cancer or cancer of any other site among hairdressers, manicurists, or beauticians.

KIRKLAND *et al.* (1978) found no more chromosomal abnormalities in the cultured peripheral lymphocytes of 60 professional hair colourists than in those of 36 matched control subjects, although more abnormalities were found in women who had their own hair dyed than in those who did not. They speculated that since hairdressers wear protective gloves, they are not really exposed to hair dyes in the same way as the women who are their customers.

KINLEN *et al.* (1977) found no excess of hair dye usage among women with breast cancer as compared with matched controls. *En passant* the report of this study refers to potential snags in the interpretation of epidemiological data derived from studies of this kind. More hair-dye users than non-users over the age of 50 were or had been smokers. Also, a greater proportion of hair dye users than non-users had their first pregnancy before the age of 20.

(v) *Chemicals and other factors to which women are exposed at work*

According to the Registrar General's 1970-1972 Occupational Mortality decennial supplement, the only occupations associated with a significantly high proportional mortality ratio for cancer of the breast, are relatively sedentary in nature. They include clerks and cashiers, typists, shorthand writers, secretaries, school teachers and social workers. In none of these occupations is there likely to be exposure to a recognized carcinogen and at the present time there is no obvious explanation for the increased risk in these occupations.

CONCLUSIONS

- (1) The breast is a complex structure comprising a wide variety of cells of ectodermal and mesodermal origin. The histological appearances of cancers reflect both the kind of cell from which they originate and the special relationships which exist between the epithelial and connective tissue elements.
- (2) The wide variation of pathological appearances of breast tumours does not necessarily reflect an equally wide variation in causative factors. Nevertheless, it would be prudent to regard cancer of the breast in humans as a group of diseases rather than as a single disease entity.
- (3) It is interesting to consider the aetiology of breast cancers on the assumption that a two-stage mechanism in carcinogenesis is implicated.
- (4) Hormones switch on or switch off genetic information without altering it. In other words, they are not mutagens. The role of hormones in the causation of breast cancer therefore is likely to be one of tumour-promotion or anticarcinogenesis rather than one of tumour-initiation.
- (5) Endogenous oestrogens probably act to promote breast cancer since early menarche and late menopause are associated with increased risk and oöphorectomy with decreased risk. However, for reasons that are not understood, the tumour-promoting effect of endogenous oestrogens is reduced following the first successful pregnancy. Consequently, the shorter the interval between the menarche and the first successful pregnancy, the lower the risk of breast cancer.
- (6) So far there is no evidence that exogenous oestrogens taken in the form of the contraceptive pill, increase the risk of breast cancer. However, it may be too early for a slightly increased level of risk to have revealed itself. There is some evidence that oestrogens given in higher doses increase breast cancer risk. In this case, nulliparous women might be more susceptible than parous women.
- (7) An earlier suspicion that drugs such as reserpine, which have the effect of increasing circulating levels of prolactin, increased breast cancer risk has not been confirmed in more recent studies.
- (8) Most research on human breast cancer has concerned the possible causative role of hormones or the hormonal characteristics of the cancer cells. Less attention has been paid to identifying agents which might be responsible for the initiation of breast cancer development. In this connection, ionizing radiation is unlikely to be an important factor, and there is no evidence in England and Wales that chemicals to which women are exposed at work are implicated.
- (9) The discovery that certain hair dye constituents are powerfully mutagenic for bacteria engendered a fear that hairdressers and women who have their hair dyed might be at increased risk of developing cancer of one or other form. If so, then the available evidence suggests that breast cancer is not one of the forms involved.
- (10) There is no substantial evidence that viruses are involved in the aetiology of human breast cancer. In this connection mammary cancer in mice would seem to be an inappropriate model for the human disease.
- (11) Female rats kept under laboratory conditions are exceedingly prone to develop both pituitary and breast tumours. They also exhibit many other manifestations of abnormal hormone status. For this reason it would be unwise to assume that mammary tumorigenesis studies in rats are necessarily relevant to man.
- (12) In the rat slight dietary restriction can profoundly reduce pituitary and mammary tumour incidence. There is some evidence that over-nutrition is an important causative factor in man. In looking for the reasons for geographical differences in breast cancer incidence attention should first be paid to diet and eating habits and the effects of these on hormonal status.

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