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Epidemiology of Breast Cancer; a Review

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THE EPIDEMIOLOGY OF BREAST CANCER FITTING THE MOSAIC

THERE have been many reviews of breast cancer epidemiology lately, and in presenting another overview I shall try to bring the various pieces together so that we may be able to grasp the present understanding of its aetiology.

DESCRIPTIVE EPIDEMIOLOGY

The outstanding feature in all descriptive papers is the large international variation in incidence, with very high rates in the richest part of the so-called 'Western' world, *viz.* North America, North Western Europe, Australia and New Zealand, and a low incidence in Africa, the Middle East and Asia. Latin America and Southern and Eastern Europe take an intermediate position [1].

There are striking differences within countries: e.g. South Africa, Israel, Poland, Brazil and also the Soviet Union [2], which are compatible with the hypothesis that breast cancer somehow is a disease of socio-economic 'Westernisation' and affluence. The recent appearance of Vol. IV in the series of *Cancer Incidence in Five Continents* documents this again.

It is now some 17 years ago since the first volume appeared and studies of time trends have become possible on a global scale. These are very welcome since mortality statistics begin to lose some of their significance. The reason for this is a healthy one: prognosis is improving due to greater awareness of the nature of breast lumps by educated people whereas chemotherapy is improving survival, mainly by delaying death.

Some countries have shown marked increases in breast cancer incidence over the last 20 yr. The most striking example is Hawaii, once a group of forgotten islands in a vast ocean. Today Honolulu is a busy melting pot of cultures with a strong American influence. The Japanese migrants of the beginning of this century have seen their children and grandchildren become American citizens with new standards and values. Their disease pattern has changed, mammary cancer showing no less than an explosion of incidence (Fig. 1). This went in a cohort-wise manner, beginning with the birth cohort of about the year 1905 (Fig. 2). This cohort-wise kind of change has also been documented in Iceland, where the 20th century saw a dramatic increase [3]. It is, however, not the only way in which incidence can increase. For example, a recent report from Australia [4] tells us that time trends affected each age group in the same calendar period.

Not only the Japanese Hawaiians underwent the strong influence of the American way of life.

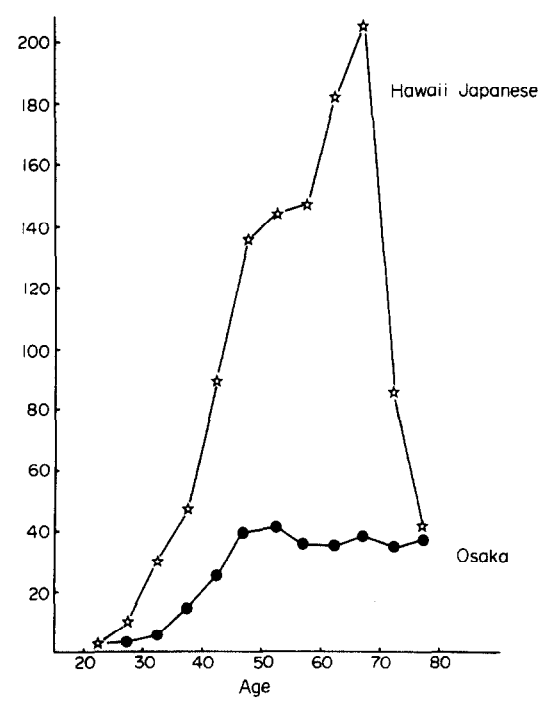

Fig. 1. Age-specific incidence (cross-sectional) of breast cancer among American women of Japanese descent in Hawaii and in Osaka, Japan.

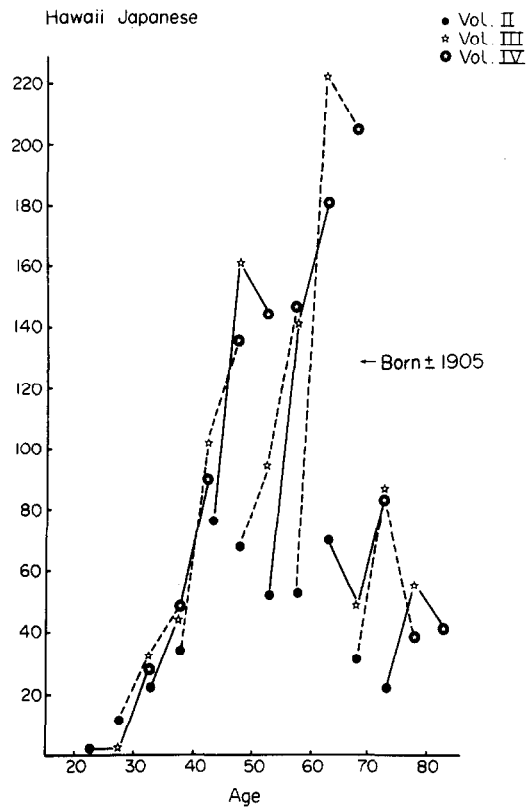

Fig. 2. Construction of age-specific breast cancer incidence as experienced by successive birth cohorts of American women of Japanese descent in Hawaii. Data from Cancer Incidence in Five Continents, *Vols II, III and IV. Since these volumes appear with 5-yr intervals the 40–44-yr-old women of Vol. II belong to the same cohort as these aged 45–49 in Vol. III and also as those aged 50–54 in Vol. IV, etc. Cohorts born before 1905 did not experience a rise in incidence after age 60.*

The descendants of the original population had their share of affluence as well and they have the rather unpleasant privilege of leading the world in breast cancer incidence, closely followed by mainland United States and The Netherlands [1, 5]. Those who have read a little Hawaiian history [6] know that Queen Alii Nui in the early 19th century was a very tall and obese woman, and the present-day traveller finds a great many women looking very royal indeed; their ponderosity has been documented [7].

In almost all reviews a point is made of the peculiar shape of the cross-sectional age-specific incidence curve in various parts of the world. In all countries there is an increase with age in premenopausal years, even though the slope is steeper in Western countries with high overall incidence. Around age 50 a break occurs: in countries with a low incidence the curve flattens to an almost horizontal course, whereas in countries with an intermediate or high incidence the curve regains its upward course, with its slope depending on the level of affluence in the country concerned.

Recently Moolgavkar *et al.* [8] have challenged the idea that cross-sectional curves can teach us anything; in fact they feel that these are misleading and that the levelling-off phenomenon at postmenopausal age in low-incidence countries is an artifact: a cohort effect. They base their statement on a study with a mathematical model using data arranged cohort-wise from six regions. Among these six the only non-Western region is the city of Osaka, Japan. It is well-known that the incidence of breast cancer in Japanese cities is rising (Fig. 3) and it is therefore clear that by drawing incidence curves which represent recent experience of birth cohorts instead of cross-sectional curves, incidence also tends to increase with age in postmenopausal Japanese women.

It is to be regretted that Moolgavkar *et al.* [8] draw inferences from their model which go far beyond their data. They ignore the data from those low-incidence countries where there is no rise in incidence. With the appearance of Vol. IV of *Cancer Incidence in Five Continents* it is now possible to draw some incidence curves from such populations cohort-wise (Figs 4, 5). In rural Poland and Bombay such curves do not show an

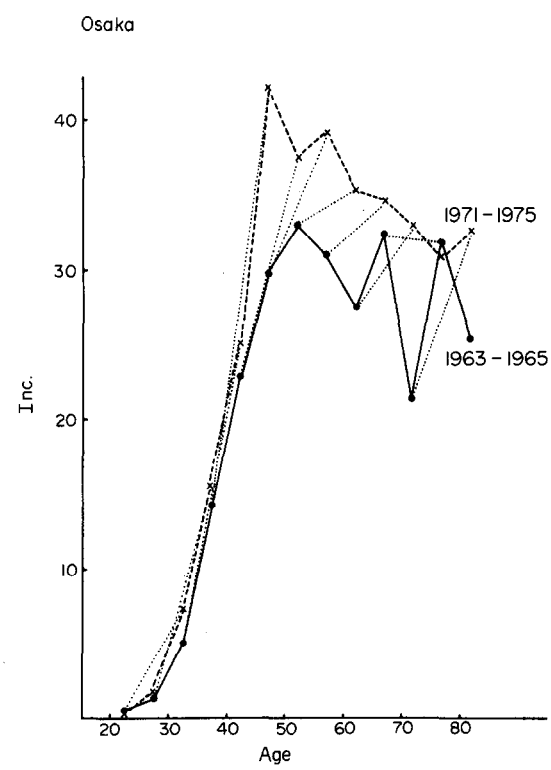

Fig. 3. Age-specific incidence curves of breast cancer (cross-sectional) in Osaka, Japan in the calendar periods 1963–1965 and 1971–1975 respectively. These curves are interconnected by dotted lines, which represent parts of cohort-wise-arranged incidence curves. The rise of the latter at all ages led Moolgavkar et al. [8] *to their hypothesis of a universally similar shape of breast cancer incidence in all continents, an idea which is being challenged in the present paper.*

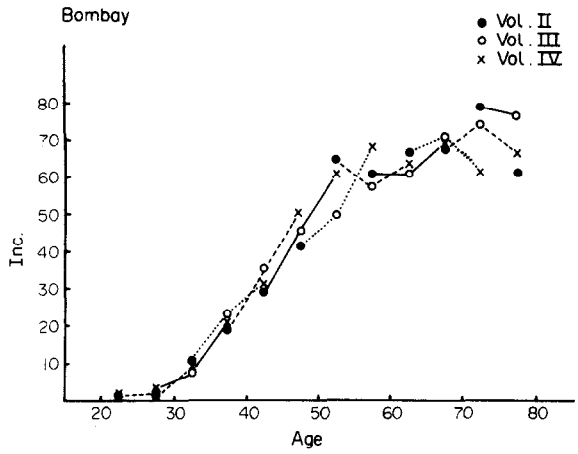

Fig. 4. Breast cancer incidence trends in Bombay. Explanation of way in which points are connected similar to that of Fig. 2.

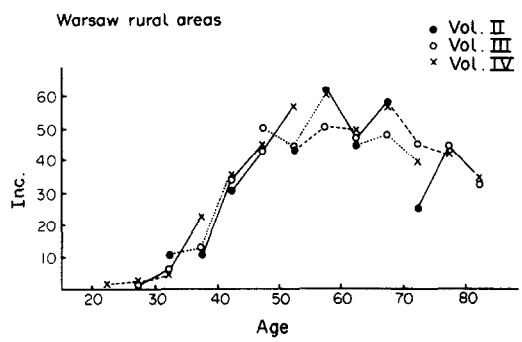

Fig. 5. Breast cancer incidence trends in rural areas of Warsaw province. Explanation of curves similar to those of Fig. 2.

increase of incidence with age after age 55. A longer period of time is needed to provide more definitive figures, assuming that economic conditions in these areas remain what they are so that incidence remains stable.

In elaborating his argument, Day [9] includes the cross-sectional age-specific breast cancer mortality curve from the beautifully edited atlas on cancer of the Chinese People's Republic. This curve runs upward at postmenopausal age, the implicit conclusion being that the incidence curve in China will do the same. However, this is not true, as was shown at the Maastricht conference on breast cancer by Shu-Ling Li [personal communication] for the regions of Beijing and Tianjin. In fact, Lin *et al.* [10] had already commented upon the discrepancy between breast cancer incidence and mortality curves in Japan and Taiwan, suggesting that they reflect a low case fatality rate or an unusually prolonged course of illness prior to death, or both.

So much for the interpretation of incidence curves. The issue remains how valid the Moolgavkar model is. The problem for the non-mathematician is that he has simply to believe what is put before him.

Fortunately Moolgavkar *et al.* [8] have reported their sources of incidence data, one of them being the Danish cancer registry which covers the period 1943–1977. Using exactly the same data (Moolgavkar's Table 1), I have plotted the cohort-bound curves on graph paper (Fig. 6). It will be seen that in Denmark the 5-yr birth cohorts born before 1890 (mid-year 1888) experienced no rise in breast cancer incidence after age 50. Apparently the mathematical model was insensitive to this phenomenon.

ANALYTIC EPIDEMIOLOGY

Having described the incidence pattern, we shall now make an effort to explain it.

Migrant studies have made it clear that environmental factors are paramount. Nevertheless, there is a familial risk which is probably of genetic origin. Tulinius *et al.* [11] have carried out a nationwide study in Iceland based on nearly the total breast cancer experience over the 20th century, which has produced estimates of the

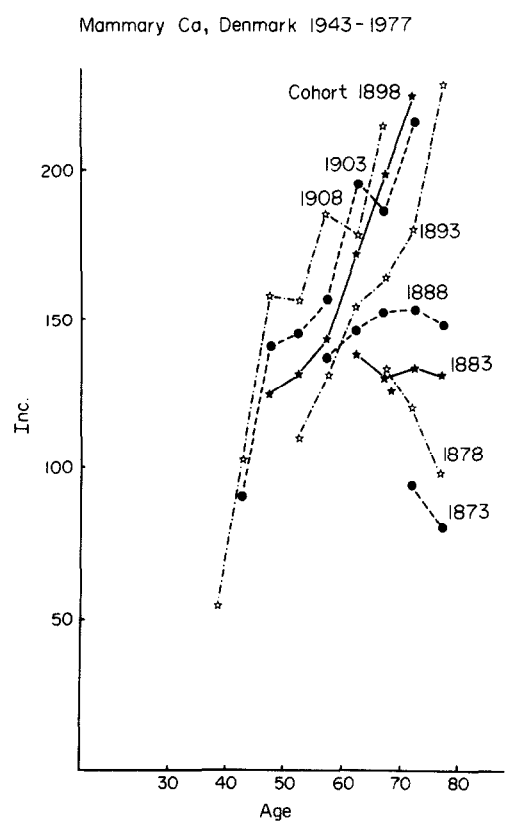

Fig. 6. Age-specific breast cancer incidence in Denmark, by birth cohorts. Data from the Danish cancer registry; see also Moolgavkar et al. [8]. *In those born before* 1890 *there is no increase in incidence between age* 55 *and* 80.

relative risk of breast cancer if either the mother or a sister has had the disease. This estimate, freed of confounding influences by parity and age at first birth, was about 2.5.

In some families breast cancer seems to concentrate. Mulvihill *et al.* [12] have considered the question of whether doctors should take an active role in helping such families in terms of prophylactic surgery. On the basis of their experience they recommend individual counseling of high-risk women.

REPRODUCTION

In sorting out the environmental factors a usual distinction is between the reproductive and the nutritional factors. The former category is made up of the following risk factors: low parity and old age at first birth; early menarche and late menopause; a history of oophorectomy has a protective effect, whereas lactation very probably has not.

Regarding parity and age at first birth, MacMahon *et al.* [13], in their international study, tended to substitute the latter for the former. However, a number of papers have challenged the conclusion, claiming an independent effect for parity. In fact, the MacMahon paper did not rule out some modest role for it, but as time went by this effect was incorrectly played down.

There is nothing wrong with these related variables acting side-by-side. Together they constitute a biologically meaningful factor, *viz.* they determine how long a woman will be protected by the effects of pregnancy. Each pregnancy leaves a mark in the breast and the earlier the first mark is placed the better.

MacMahon *et al.* [13] reached this conclusion in 1970 on pure statistical-epidemiologic grounds. Recently we came to understand this biologically in an epidemiologic study of Wolfe's so-called mammographic patterns. Wolfe [14] described the radiologic features of 'dysplasia (DY)' and 'prominent duct pattern (PDP)', which he claimed to be associated with a high breast cancer risk. Although he may have overstated the degree of risk, several others have confirmed his idea in a qualitative way.

In a large population-based screening programme on women aged 50 and over, our group at Utrecht University classified more than 23,000 xeromammograms according to the presence or absence of both these radiologic patterns.

Ignorant of some earlier hints as to a relationship between the breast parenchymal pattern and age at first birth [15], we studied this kind of relationship, including parity as well. A striking dose–response relation was found between both reproductive variables and both aspects of breast structure. Parity and age at first birth had joint effects as well as independent effects on the occurrence of DY and on PDP.

These observations, based on a large and virtually unselected population, are thought to be the 'missing link' between parity and age at first full-term pregnancy on the one hand and breast cancer risk on the other. These parenchymal patterns have been shown by Wellings and Wolfe [16] to be associated with an increased prevalence of atypical lobules (ALA), and these again are considered precancerous lesions.

Our observations prove the point that a first pregnancy leaves a mark in the breast, *viz.* it tends to prevent or postpone the occurrence of atypical lobules, each successive pregnancy adding some extra protection. One cannot but endorse the view put forward by Russo *et al.* [17] that pregnancy does this by inducing differentiation of mammary cells.

A relatively new member in the family of aetiologic hypotheses regarding reproduction and breast cancer was the concept of luteal insufficiency. It was first published by the Italian endocrinologist Grattarola [18] and propagated by the French endocrinologists Mauvais-Jarvis *et al.* [19]. In the United States Korenman [20] enlarged it by including not only the premenopausal years of anovulation but also postmenarcheal years of ovarian ripening without proper luteal function (the 'two-window hypothesis').

Meanwhile the window at young age has been partly closed. We and others [21, 22] have shown that in girls with early menarche there is no enlarged time period of anovulation. Thus we are back at the second window. Cowan *et al.* [2°] and Coulam [24] have reported an increased risk associated with anovulation.

In the framework of a recently initiated population-based screening project aiming at the early detection of breast cancer in a cohort of over 10,000 women between 40 and 49 yr of age, we hope to settle this issue once and for all. These women have agreed to keep a menstrual calendar and to provide us with a 12-hr specimen of urine on day 22 of 3 consecutive menstrual cycles. These specimens are stored in a large deep-freeze. After having delivered their third specimen the women are screened and followed up by means of a cancer registry. We expect to resolve this issue by 1985.

NUTRITION

Menarche and menopause are usually described under the heading of reproduction. There is, however, nothing against including them under nutrition, since both are affected by nutritional status, particularly body weight [25].

There are two schools of thought regarding the kind of 'Western' nutritional factor that influences the incidence of breast cancer. Wynder and Cohen [26] point towards the deleterious effects of high fat intake, whereas our group focuses on the dangers of overweight. Both groups build on experimental and epidemiologic evidence. Interestingly, the issue may be decided in clinical medicine since both schools recommend clinical trials which should show whether dietary intervention as a form of adjuvant therapy in primary treatment of breast cancer will improve prognosis [26, 27]. The rationale is that nutrition seems to be a promotor of tumour growth. Thus slowing down the rate of growth will be both treatment and prevention. Since preventive trials are far too costly the curative trial will have to be relied upon to give the answer.

For those clinicians who have been induced recently to treat patients with chemotherapy these proposals may seem fantastic. However, they are not. The effect of obesity on prognosis has been documented in three studies [26, 27] and the effect of dietary intervention in experimental breast cancer is immediate [28]. It should be pointed out that breast cancer mortality in England and Wales began to fall immediately after rationing was introduced in 1939–1940; it began to increase again in 1958 and was back to its original level in 1970 [29].

The effect of obesity is limited to post-menopausal years and it is almost certainly mediated by extra-ovarian oestrogens, as we have shown in a population-based study of oestrogen-receptor-positive and -negative breast cancer [30]. Oestrogen-receptor-positive (ER+) breast cancer cells apparently thrive only in moderately or grossly obese women, whereas in lean women they do not; eventually by means of clonal selection the cancer will turn into an ER- tumour. Japanese experience has shown that ER-negativity is not necessarily a bad sign prognostically.

CONCLUSION

What have we learned from epidemiology to date? I think a great deal. I do not think that we need to search for new risk factors.

Most of the risk factors are no longer vague statistical notions. They can be understood biologically. Ionising radiation can initiate malignant transformation [31]. There is considerable evidence to incriminate oestrogens as potential tumour promotors. Whether they do this depends largely on other endocrine factors. Hormones produced by the placenta and the corpus luteum seem to protect against breast cancer. Studies about possible dangers of drug use have not revealed risks [32], with the possible exception of small effects of oestrogens and reserpine. The contraceptive pill is safe as regards breast cancer [33], possibly due to its progestational component.

In terms of life-style I am very close to recommending two things from a primary prevention point of view: (1) do not delay in getting your first baby, and do not limit your family to one child only; and (2) limit calorific intake (preferably by cutting down fat consumption) and fight obesity. There may be other possible recommendations related to the use of oestrogenic drugs and anovulation, but these are probably minor compared with the two major issues.

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