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Hypothesis

ŒSTROGEN FRACTIONS DURING EARLY REPRODUCTIVE LIFE IN THE ÆTIOLOGY OF BREAST CANCER

Summary Experimental studies have shown that, when combinations of the œstrogen fractions are administered, the net effect is influenced by the relative amounts of the several fractions as well as by the total dose. Specifically, it appears that the non-carcinogenic, impeded fraction (œstriol) partly inhibits the action of the carcinogenic, unimpeded fractions (œstrone, œstradiol). However, attempts to demonstrate differences in the ratio of impeded to unimpeded œstrogens between breast cancer cases and controls have been inconclusive. Epidemiological evidence suggests that early reproductive life is a time when events of significance to future breast-cancer risk occur. In particular, pregnancy at a young age is associated with both favourable œstrogen fraction ratios and decreased breast-cancer risk. We therefore suggest that the relative levels of the individual œstrogen fractions produced in the first decade or so after puberty are important determinants of a woman's life-time breast-cancer risk. This hypothesis allows reconciliation of several sets of observations which have previously seemed inconsistent, including the varied results of case-control studies. While a direct test of this hypothesis is not likely to be forthcoming in the next decade, several investigations could be undertaken immediately to provide persuasive evidence for or against it.

BACKGROUND

In the search for measures to prevent breast cancer, three epidemiological features of the disease stand out because of the extent of the variation in risk which they reveal:

1. The reduction in risk experienced by women who undergo oophorectomy before the age of 40.[1]
2. The life-long reduction in risk associated with pregnancy,[2] particularly pregnancy at an early age.[3,4]
3. The low incidence of breast cancer in Japan and other Asian and African countries.[5]

The first observation supports the belief that the ovarian hormones play a major role in the induction or maintainance of human breast cancer. Such a role had previously been inferred from the therapeutic effect of oophorectomy in some women with the established disease, and from a substantial accumulation of work with experimental animals.[6] We are now faced with the intriguing problem of reconciling this obvious role of the ovary with the other epidemiological features. It seems paradoxical that the greatly increased production of ovarian hormones during pregnancy should be associated with decreased, rather than increased, risk of breast cancer. If the low breast-cancer rate in Asia is to be explained by the same model, we must account for the relative carcinogenicity of the American and North European ovary in terms of some special characteristic rather than its principal functions, since the femininity of Asian women is undeniable.

Certain other epidemiological observations point to causal factors operating long before the appearance of clinical cancer. It is generally recognised that induction periods for human neoplasia must be measured in decades, but specifically in breast cancer the significance of the early years of life is suggested by: (1) the fact that the increase in incidence seen in British and American women born since 1900 has occurred in a fashion characteristic of their year of birth, rather than of the years in which their breast cancer becomes manifest[7]; and (2) the retention by Japanese migrants to the United States and their daughters of the low incidence characteristic of Japan.[8] That the early reproductive ages are particularly important is suggested by the association of breast-cancer risk with age at first pregnancy. Pregnancies over the age of 25 appear not to exert any protective effect, and women first pregnant before age 20 have about half the risk of those first pregnant after 25 years of age.[9]

Turning to the endocrinological background, it has been shown that women produce three œstrogen fractions in substantial amounts—œstrone, œstradiol, and œstriol. During the follicular phase of the menstrual cycle most œstrogen is synthesised in the form of œstradiol. This is in part converted to œstrone in a reversible reaction which establishes an equilibrium between the two. Œstriol is produced almost entirely from the irreversible metabolism of œstrone and œstradiol. During the luteal phase of the cycle, while production of the other two fractions continues relatively unchanged, the œstriol level increases substantially as the result of its direct synthesis, probably by the corpus luteum.[10] During pregnancy there is an overwhelming rise in the total œstrogen output, œstriol being increased to a relatively much greater extent than are the other two fractions.

Differences have been demonstrated in the carcinogenic potential of the three œstrogens, œstrone being a more powerful carcinogen than œstradiol, and œstriol not having been shown to be carcinogenic.[11,12] Furthermore, it has been shown that the presence of œstriol inhibits the uterine growth-promoting effects of the more active fractions and that the relative amounts of these three fractions, as well as the total level of œstrogens, are important determinants of the net effect.[13] While this inhibiting effect has not been demonstrated for carcinogenicity specifically, Lemon and his colleagues suggested that women in whom the ratio of œstriol to the other fractions is low might be at high risk of breast cancer.[14] These workers studied this ratio in a series of breast-cancer cases and controls and found lower values in the cases. However, others have found higher values among cases than among controls.[15,16] The

1. Feinleib, M. *J. natn Cancer Inst.* 1968, **41**, 315.
2. Logan, W. P. D. *Lancet*, 1953, ii, 1199.
3. Salber, E. J., Trichopoulos, D., MacMahon, B. *J. natn Cancer Inst.* (in the press).
4. Valaoras, V. G., MacMahon, B., Trichopoulos, D., Polychronopoulou, A. *Int. J. Cancer* (in the press).
5. Doll, R., Payne, P., Waterhouse, J. Cancer Incidence in Five Continents. New York 1966.
6. Huseby, R. A. *in* Methods in Hormone Research (edited by R. I. Dorfman); vol. iv, p. 123. London, 1965.
7. MacMahon, B. *Cancer, N.Y.* 1957, **10**, 1037.
8. Haenszel, W., Kurihara, M. *J. natn Cancer Inst.* 1968, **40**, 43.
9. Unpublished data, international collaborative study of breast cancer. Department of Epidemiology, Harvard School of Public Health.
10. Barlow, J. J., Logan, C. M. *Steroids*, 1966, **7**, 309.
11. Hartwell, J. Survey of Compounds Which Have Been Tested for Carcinogenic Activity. Washington, 1951.
12. Shubik, P., Hartwell, J. L. Survey of Compounds Which Have Been Tested for Carinogenic Activity. Washington, 1957.
13. Huggins, C., Jensen, E. V. *J. exp. Med.* 1955, **102**, 335.
14. Lemon, H. M., Wotiz, H. H., Parsons, L., Mozden, P. J. *J. Am. med. Ass.* 1966, **196**, 112.
15. Grönroos, M., Aho, A. J. *Europ. J. Cancer*, 1968, **4**, 523.
16. Marmorston, J., Crowley, L. G., Myers, S. M., Stern, E., Hopkins, C. E. *Am. J. Obstet. Gynec.* 1965, **92**, 460.

studies reported to date can be criticised on the basis of haphazard selection of subjects, and the numbers of observations have been insufficient to deal adequately with the considerable variation in the œstrogen profile.[17 18] The fact that some breast tumours themselves produce œstriol [19] is a further confounding factor. For these reasons, the question of whether breast-cancer patients do show a disturbance in the ratio of the œstrogen fractions must be considered still open. However, the overall impression from the studies reported to date is that differences between cases and controls, if they exist, are likely to be too small to provide a firm substantiation of the hypothesis proposed by Lemon and his colleagues.

Thus, while both the epidemiological and endocrinological approaches have raised interesting questions, neither has provided a useful model for the ætiology of this disease—much less any hint of a practical preventive measure.

THE HYPOTHESIS

Combining the observations from these two fields, we suggest that the relative levels of the œstrogen fractions produced between puberty and about the 25th year of age are crucial determinants of a woman's lifetime breast-cancer risk.

One can envisage several ways in which an unfavourable ratio of the fractions may come about. Levels of the more carcinogenic fractions, such as œstrone, may be high, or levels of œstriol may be low. For individual women œstriol levels may tend to be low at all times, during the follicular phase only, during the relatively protected luteal phase only, or during pregnancy. We must also acknowledge the complexity of interaction between ovarian and other endocrine systems and the many mechanisms whereby œstrogen balance may be disturbed. The concept we propose is not specific as to the mechanism of production of the unfavourable ratios. We suggest only that, taking this 10–12-year period as a whole, a shift in the ratios of the levels of the œstrogen fractions towards those more carcinogenic is associated with a life-time increase in breast-cancer risk.

To be useful, a hypothesis must account for observations which were not explained, or not so adequately explained, in its absence. The following are features of breast cancer that are accounted for by this hypothesis:

1. The experimental, clinical, and epidemiological evidence pointing to the importance of the ovary in this disease.

2. The epidemiological evidence already referred to indicating the significance of the experiences of early life in the determination of breast-cancer risk.

3. The paradoxical reduction in risk associated with pregnancy. As noted by Wotiz et al.,[20] this is readily explained by the fact that during pregnancy œstriol is increased to a much greater extent than the other œstrogens.

4. A second paradox developing from the fact that, while pregnancy in humans is protective, pregnancy in mice increases the risk of breast cancer.[21] The hypothesis resolves this apparent inconsistency since the pregnant mouse produces œstrone and œstradiol,[22] but no œstriol.[23]

5. The hypothesis may also explain the inconclusive results of case-control studies of œstriol/œstrone ratios in breast-cancer patients. If the significant hormonal relationships are those of early reproductive life they may or may not be reflected in the hormone patterns seen in the age-groups in which the breast cancer becomes manifest. Furthermore, differences between individuals in the degree of protection gained during pregnancy obviously will not be revealed in studies done years later.

While each of these features can also be explained in other ways, we are unaware of any alternative hypothesis that accommodates them all.

A hypothesis is also more tenable if a plausible mechanism can be cited in its support. The work of Dao, and more recently that of Wotiz et al., have provided this, at least for that component of the concept which invokes the relative levels of the œstrogen fractions. Dao's work with the rat suggested that the incorporation of a potent mammary carcinogen by the breast was impeded by the relatively less carcinogenic, but more abundant, hormones of pregnancy.[24] Wotiz et al. showed that exogenous œstriol blocked the nuclear incorporation of œstradiol by uterine cells and, possibly, by isolated cells from a breast tumour.[20] A likely mechanism for both sets of observations is that compounds of different carcinogenic potential compete for binding sites at the molecular level.

A mechanism to account for the significance of the early reproductive years is more difficult to identify. The fact that the age under suspicion is 20–50 years prior to the usual appearance of cancer suggests that the mechanism pertains to tumour induction, rather than maintenance. This, of course, does not exclude the existence of œstrogen effects on tumour maintenance, for it is well known that most agents capable of tumour induction also act as promoting agents, and vice versa. Since most oophorectomies are performed in women over 30 years of age, the reduction in the risk of breast cancer among oophorectomised women must be accounted for primarily by mechanisms other than those relevant to this hypothesis. However, there are reasons to suspect that part of this reduction in risk may be due to change in œstrogen fraction balance: (1) the protective effect is particularly strong after oophorectomy in younger women [3]; (2) the adrenal gland, which can produce large amounts of œstrogen in young oophorectomised women, elaborates relatively large amounts of œstriol.[25 26] Of course, some women do undergo oophorectomy during the period of high risk of tumour induction; the age at which this period ends no doubt varies, and in some individuals may extend beyond the middle 20s. In any event, a satisfactory explanation of the postulated long incubation period of breast cancer is not available, as with other human tumours in which equally long incubation periods have been clearly demonstrated.

SIGNIFICANCE

We have so far considered this hypothesis as a basis for understanding certain experimental and epidemio-

17. Paulsen, C. A. (editor) Estrogen Assays in Clinical Medicine. Seattle, 1964.
18. Schweppe, J. S., Jungman, R. A., Lewis, I. *Cancer, N.Y.* 1967, **20**, 155.
19. Adams, J. B., Wong, M. S. *Lancet*, 1968, ii, 1163.
20. Wotiz, H. H., Shane, J. A., Vigersky, R., Brecher, P. I. *in* Prognostic Factors in Breast Cancer (edited by A. P. M. Forrest and P. B. Kunkler); p. 368. London, 1968.
21. Mühlbock, O. *in* Advances in Cancer Research (edited by J. P. Greenstein and A. Haddow); vol. IV, p. 371. New York, 1956.
22. Velle, W. *in* Comparative Endocrinology (edited by U. S. von Euler and H. Heller); vol. I, p. 133. London, 1963.
23. Pearlman, W. H. *in* The Hormones (edited by G. Pincus and K. V. Thimann); vol. I, p. 351. London, 1948.
24. Dao, T. L. *in* On Cancer and Hormones: Essays in Experimental Biology (edited by A. Haddow); p. 231. London, 1962.
25. Barlow, J. J. *J. clin. Endocr.* 1964, **24**, 586.
26. Persson, B. H., Risholm, L. *Acta endocr., Copenh.* 1964, **47**, 15.

logical observations. While this provides its scientific interest, it is not where the practical significance lies.

If confirmed, the concept offers the possibility of identifying, during their early reproductive years, a group of women at high risk of breast cancer, and of instituting preventive measures by changing their œstrogen profiles with exogenous hormones. The institution of practical preventive measures, as distinct from the mere identification of high-risk women, will require the use of one or more œstrogen fractions having little or no carcinogenic potential when given in doses adequate to sustain normal function. While some investigators have expressed the view that the differences in carcinogenicity of the œstrogen fractions merely reflect differences in "œstrogen activity", there are grounds for believing that the diverse effects of these compounds are separable, at least quantitatively.[27 28] The differences in their chemical structures alone are sufficient to suggest specialisation of function. In addition, differential potencies between the fractions are clearly evident with respect to water retention, tissue growth, and other components of the complex of activities subsumed under the term "œstrogen activity".[29] More directly, the idea that carcinogenicity is an inseparable property of "œstrogenicity" is contradicted by the empiric observation that, on an equimolecular basis, œstradiol is the most potent "œstrogen"[27] whereas œstrone is the most potent carcinogen.[11 30]

The hypothesis also has implications for the selection of the œstrogen to be used in oral contraceptives. All oral contraceptives now commercially available in the United States use ethynyl-œstradiol or its 3-methoxy congener. This compound has definite carcinogenic potential, having produced tumours of both breast and liver in experimental animals.[11 12] While œstriol and its derivatives have been shunned, presumably because of weak œstrogenic activity, this weakness may in fact be advantageous if inhibition of ovulation requires large doses which simultaneously inhibit the carcinogenic activity of endogenous œstrogens.

TESTING THE HYPOTHESIS

As noted previously, attempts to test the relevance of the œstrogen fraction ratios to human breast-cancer risk have focused on comparison of affected and unaffected women. The addition of the concept of a specific age-of-risk to the model increases the practical problems of providing a direct test of the hypothesis. A large group of young women will have to be followed over a long period of time after their œstrogen profiles have been determined. The determinations can at present be made only on a 24-hour urine (not the easiest specimen to collect), and the chemical procedures are technically complex and expensive. Furthermore, the issue cannot be approached by studies in which urines are stored and retrieved for analysis after the identification of the cancer patients, since œstrogens deteriorate in stored urine. The significance of the disease warrants the economic and professional investment required, but, since the question cannot be investigated retrospectively, there seems to be no way to circumvent the inevitably long follow-up period. It therefore seems unlikely that a direct test of the concept can be provided in humans within the next decade or so.

Nevertheless, there are several investigations which would allow indirect evaluation of the hypothesis. Results of these may be sufficient to discard the idea or to encourage greatly augmented efforts to provide the direct test. These investigations include the following:

1. Study of the age trend in the ratios of specific œstrogen fractions in women in the reproductive ages. Since breast-cancer risk increases with increasing age at pregnancy, we would predict, under the hypothesis, that either (*a*) relatively unfavourable ratios of œstrogen fractions exist among non-pregnant women in the younger ages (pregnancies at young ages would then be exerting their protective effect during a period of particularly high risk) or (*b*) the degree of protection conferred by the favourable œstrogen ratio of pregnancy decreases with age. Several investigations have shown lower œstriol titres for premenopausal than for postmenopausal women [20]—a trend which if it could be extrapolated to the younger ages would support the hypothesis. However, there are no published data on the variation of œstrogen profiles with age during the reproductive years, either in pregnant or in non-pregnant women.

2. Comparison of the œstrogen profiles of young women of different nationalities—particularly Japanese and American. Bulbrook et al. compared the ratios of two androgens in British and Japanese women and found a difference.[31] However, in regard to œstrogen fractions, there are, in English-language and Japanese reports, only two relevant studies of Japanese women—each based on ten or fewer subjects.[32 33] The results of these studies are compatible with the hypothesis—the reported ratios of œstriol to œstrone are roughtly twice as high as in American and British reports. But it is not clear whether the analytical methods used are comparable; nor are the numbers of subjects sufficient to warrant confidence in the differences observed.

3. Case-control studies of women with chronic cystic mastitis. Epidemiological similarities, as well as clinical association,[34] between cystic mastitis and breast cancer suggest that the two conditions may have a common hormonal predisposition. Since cystic mastitis appears at a younger age than does breast cancer, patients with the former disease—particularly the younger patients—may more accurately portray the hormone pattern of ætiological significance.

There is also need for a large and carefully designed case-control study of the œstrogen fractions in breast-cancer patients. However, it is important to note that, for the reasons indicated above, failure to find differences between cases and controls even in a definitive study would not invalidate the hypothesis.

These evaluatory studies would be facilitated by more rapid and accurate methods of œstrogen determination. Methods which would allow urinary œstrogens to be stored and the development of a method for accurate estimation of circulating œstrogens would be of great value. Nevertheless, the studies proposed are by no means beyond the capability of existing methods and resources.

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27. Emmens, C. W., Martin, L. *in* Methods in Hormone Research (edited by R. I. Dorfman); vol. III, p. 1. London, 1964.
28. Hisaw, F. L., Jr. *Endocrinology*, 1959, **64**, 276.
29. Turner, C. D. General Endocrinology. London, 1966.
30. Pullinger, B. D. *Br. J. Cancer*, 1961, **15**, 574.
31. Bulbrook, R. D., Thomas, B. S., Utsunomiya, J. *Nature, Lond.* 1964, **201**, 189.
32. Matsumoto, S. Nihon Sanka Fuzinka Gakkai Hokoku-Yoshi. Gumma, 1962.
33. Matsumoto, K., Seki, T. *Endocrinol. Japan*, 1963, **10**, 183.
34. Warren, S. *Surgery, Gynec. Obst.* 1940, **71**, 257.