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LATE MENOPAUSE AND CANCER OF THE BREAST

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Several observers have suggested that a positive relationship may exist between the occurrence of menopause at an advanced age and the development of cancer in the tissues of the female reproductive organs. Thus Crossen and Hobbs (1) state that "the incidence of late menopause in cases of adenocarcinoma of the fundus uteri is about four times as high as it is in normal cases," while Olch (2) finds a similar relationship between a delayed menopausal age and cancer of the breast. Among his cases of 342 women suffering from breast cancer, and first coming to medical attention after the age of fifty, Olch's records showed that 187, or 54.7 per cent, were either still menstruating or had stopped after fifty. In Olch's opinion this was about five times the proportion to be expected, accepting as "normal" the figures cited in literature on the age at menopause among women in temperate climates, which in various series appears to be fifty years or more in only nine to twelve per cent, or an average of eleven per cent of all the cases.

Many experiments with animals have established the fact of hormonal (estrogen) action in the production of mammary tumors and certain tumors of the body of the uterus. (3) (4) Thus it is quite conceivable that the prolonged hormonal stimulation incident to delayed menopause may be related to the development of malignancies in genital tissues. However, the question whether a delayed menopause actually coincides with an increased incidence of cancer of the breast and the corpus uteri is not only of theoretical interest in the study of tumor genesis, but is of great practical importance. For at least in connection with breast cancer it has already been recommended that "a prophylactic artificial menopause should be proposed to those women menstruating beyond any arbitrary age that we may choose, forty-eight or fifty, whether or not those women have palpable breast changes." (2)

The next question is whether the evidence for a direct relationship between late menopause and the development of malignancies in breast or uterus is statistically so conclusive that such a procedure is warranted. Crossen and Hobbs (1) have rightly warned against "certain pitfalls in gathering statistics on normal menopause which have not been taken into account in the compilation of statistics in the present day literature." One such pitfall lies in the use of antiquated data to arrive at a so-called "normal" menopausal age. For it is the impression of many experienced physicians and statisticians that during the last few decades the menstrual cycle has changed its range considerably in many countries, so that figures gathered fifty or seventy years ago cannot be accepted as a basis for judging conditions today.

But from still another viewpoint the conclusion drawn from Olch's material does not seem to be quite valid, at least as to specific estrogenic action on cancer of

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the breast, in the absence of comparative data on the incidence of cancer of other sites collected from a similar population. The writer has therefore attempted to secure further evidence on this problem by comparing the conditions found in a series of cases of breast cancer with those in a series of cases of cancer in tissues not usually assumed to be under ovarian influence, such as the skin, the lips, the tongue, and the gastrointestinal tract. The investigation was confined to mammary cancer because of the comparatively rare incidence of carcinoma of the body of the uterus. Further it appeared desirable to compare the distribution of menopausal age among cancer patients with that among women in a general hospital, suffering from various non-cancerous conditions, whether under surgical or general medical care.

The three series of cases were drawn from medical records in the Columbus Cancer Clinic, and the Ohio State University Hospital, and may be presumed to be largely homogeneous, from the environmental point of view. The author is deeply indebted to the officers of these two institutions for their courtesy and co-operation in this investigation as well as to Dr. Earl L. Green, of the Ohio State University, for his statistical advice.

METHOD AND PROCEDURE

In drawing the cases from the files of clinic and hospital, the common principle of selection was that the patient should have been admitted when at least fifty; that information was available as to the age at menopause (i. e., the final cessation of the menstrual flow); and that there was no history of previous pelvic operation. Otherwise these were random samples compiled from the records of 1921-1941.

TABLE I

AGE AT MENOPAUSE REPORTED BY THREE GROUPS OF PATIENTS WITH (I) CANCER OF BREAST, (II) CANCER OF NON-GENITAL TISSUES, AND (III) CONDITIONS OTHER THAN CANCER. (Columbus, Ohio, 1941.)

REPORTED AGE AT MENOPAUSE	SAMPLE I Breast Cancer		SAMPLE II Non-genital Cancer		SAMPLE III Other than Cancer	
	No.	%	No.	%	No.	%
Under 40.....	3	2.0	4	2.4	3	5.0
40-44.....	21	14.3	28	17.2	7	12.0
45-49.....	39	26.6	56	34.4	21	35.0
50 and over.....	84	57.1	75	46.0	29	48.0
Total.....	147	100.0	163	100.0	60	100.0

The two series from the Cancer Clinic included, in Sample I, 147 cases of cancer of the breast; and in Sample II, 163 cases of cancer of other sites, mainly "external" and all strictly non-genital and non-mammary. Sample II was made up of 128 cases of cancer of the skin, lip, and oral cavity, together with 35 cases of cancer of the gastrointestinal tract and accessory bodies such as the gall-bladder.

The age at menopause for the two groups of women is shown in Table I. From this it will be seen that the proportion of women reaching the menopause when younger than forty is about the same for the two groups, although it is a fraction larger in the group with non-genital cancer; while the proportion reaching the menopause between forty and forty-four is three points higher in the non-genital group; and between forty-five and forty-nine the non-genital group is eight points higher.

But the group with breast cancer reported menopause at fifty or over in 57 per cent of the cases, as compared with 46 per cent among the non-genital cancer group.

The figure of 57 per cent in our series of cases with breast cancer compared well with the 55 per cent cited by Olch in his series of 342 cases; and the apparently high coincidence of late menopause with cancer of the breast seemed to confirm his conclusion of a causative relationship. But later critical examination makes it appear that these figures can be accepted as establishing prolonged estrogenic action as a causative agent in the development of mammary cancer *only* if the distribution of menopausal age can be shown to be strikingly different among cases of cancer of tissues which are not usually assumed to be influenced by estrogenic action. However, as shown in Table I, among the 163 women suffering from cancer of the skin, lip, oral cavity or gastrointestinal tract, 75, or 46 per cent, likewise reached the menopause after fifty. If the 35 cases of gastrointestinal cancer are excluded, the others with purely "external" cancer show 47 per cent menstruating after fifty. But this is a figure at least four times as high as would be expected if we assume with Olch that only about eleven per cent of women are normally in this group.

Two explanations for this surprising fact suggest themselves: First, if the figure of eleven per cent—or about one in nine—is considered as a normal incidence of late menopause, the inference is that cancer of other tissues beside the genital are likewise related to a prolongation of estrogenic activity. Such a possibility cannot be disregarded in the light of discoveries in animal experimentation. Leo Loeb (3) has pointed out that in animals, carcinogenic action of the estrogens is not necessarily *specific* for the development of mammary cancer; and he and other observers have found sarcoma developed after prolonged estrogenic treatment, sometimes in regions remote from the site of the injections. Lacassagne (7, 8) e. g., has found sarcomas in the bladder and in the thymus after prolonged estrogen treatment. (See references for the more important of these findings by Leo Loeb (3); C. F. Cori (5); W. U. Gardner, G. M. Smith, L. C. Strong and E. Allen (6); A. Lacassagne (7) (8); and E. L. Burns, V. Suntzeff, and L. Loeb (9).)

It is possible therefore that prolonged estrogenic action might have been effective in the production of a high incidence of cancer of various non-genital tissues in our series of women.

However, another explanation is possible, and that is that the percentage of women who "normally" reach the menopause when fifty or older, is greater than might be assumed from figures cited in the earlier literature, so that the women with cancer of various tissues who also reach the menopause at an advanced age simply represent the common condition. If there is on the contrary a positive correlation between late menopausal age and cancer of the breast and other tissues, one is bound to find statistically significant differences in the distribution of this age among cancerous and non-cancerous cases in the same population at the same period.

To follow this lead, a third series of cases was gathered, this time from the Ohio State University Hospital, and makes up Sample III, a group of women suffering from various surgical and general conditions, all definitely non-cancerous, such as fractures, gastric ulcers, cholecystitis, arthritis, and metabolic disturbances. All cases with previous pelvic operations were excluded; and all in which there was evidence of some pelvic or endocrine condition which might have influenced the onset of menopause; and of course cases with a history indicating possible malignancy at any time were ruled out. Since the age at menopause is not recorded routinely in a general hospital, the range of choice was further limited. Finally after the examination of many hundreds of records, sixty cases were found which met all the specifications. To possible criticisms of the small size of this sample the answer is offered that a relatively few cases gathered as nearly as can be

under identical conditions offers a better basis for statistical comparison than a large number collected from a wide variety of sources in the literature of different countries and times, and representing completely disparate environmental conditions.

Subdivided according to the age at menopause, Sample III also appears in Table I. Comparing this distribution with that in Sample II, the non-genital cancer cases, one is struck by their close similarity in the groups reaching menopause at forty-five or forty-nine and after fifty.

By comparing the three samples it is clear that the breast cancer cases do not differ markedly from the other groups, although there is a lower incidence of menopause at ages younger than fifty and a considerably higher incidence of menopause at fifty or more. But, as the table clearly shows, these differences in the incidence of a late menopause in the cases of breast cancer and in the series of non-genital cancer and non-cancerous cases are not great enough to warrant conclusions as to a causative relationship between delayed menopausal age and cancer of the breast.

When a statistical comparison is made of the two percentages of women with menopause after 50, with and without breast cancer, it is found that the difference ($11.1 = 57.1 - 46.0$) is almost exactly 1.96 times its own standard error, and therefore has a 5 in 100 chance of being due to sampling fluctuation alone. Statistically therefore it cannot be interpreted either definitely in the positive or definitely in the negative. In any case, the conclusions which can be drawn from the figures given do not sufficiently support the above mentioned statements as to a true association between a late menopausal age and cancer of the breast.

For this reason it would appear that the proposal to induce an artificial menopause in cases with a delayed menopause in order to prevent mammary cancer has not as yet on a secure statistical basis.

GENERAL DISCUSSION

From a practical point of view the conclusions which may be drawn from our data are unsatisfactory, since they demonstrate only the fact that we are far from an answer to the question of the relation between late menopausal age and cancer of the breast. The author's findings in this investigation are in complete agreement with those arrived at by E. K. Dawson (10) who in his paper, "The Menopausal Age and Mammary Cancer" was able to say only that "the figures representing the age distribution of the menopause and the incidence of cancer of the breast are not *inconsistent* with the hypothesis, suggested by other considerations, that a correlation exists."

In fact, one may admit that the hypothesis of such a correlation suggests itself also from the author's present data, with the high coincidence of breast cancer and late menopausal age, 57 per cent as compared with 46 or 48 per cent in the non-genital cancerous and the non-cancerous groups, even if the difference reaches only the borderline of statistical significance. But much more work must be done before one can arrive at a safe basis for judgment.

One of the main hindrances to the solution of the problem is ignorance of the actual facts with regard to the normal age distribution at menopause. Existing statistics are for the most part antiquated, as for example the frequently cited figures of Kisch which were published in 1874 (11), those of Currier (12) (1897) and of Krieger (13) (1869); or when later figures are used, they may be drawn from scattered or inadequate sources; and insufficient account is taken of the completely different environmental conditions existing among the women in the various groups which may be under consideration, so that the figures may not be truly comparable for statistical purposes.

Other pitfalls are inherent in the method of collection and evaluation of the desired data. For example, the writer collected his age data by single years, but for this particular investigation presented them in the same classification as Olch, by five-year groups—40–44, 45–49, 50 and over—so that the results might be compared. This arrangement however is not satisfactory for statistical purposes, because of the peaks naturally occurring at the years forty, forty-five and fifty. For women are inclined to give the age at menopause in round figures, especially if several years have passed. The characteristic peak at the fiftieth year is shown very clearly in Dawson's tables (11). In his series of 244 "normal" surgical cases, the figures go as follows:

46 cases at 47 years
24 " " 48 "
24 " " 48 "
23 " " 49 "

then jump to

52 cases at 50 years

and fall again to

10 cases at 51 years
10 " " 52 "
8 " " 53 " and so on.

The author has found the same inexact memory about the age at menopause in many cases under observation; these artificial peaks at the five year or ten year intervals are familiar to all students of population statistics, making a major source of error in interpretation. But this fact is bound to have an especially important bearing on our problem, since it is precisely the year fifty which is considered the point marking a delayed or non-delayed menopause. Therefore, it is evident that the conclusions to be drawn from such investigations may depend more or less upon the way in which the year "fifty" is dealt with, i. e., whether the age groups are subdivided, e. g., in those from 40 to 44, 45 to 49, 50 and over; or whether the same material is subdivided into the groups 41 to 45, 46 to 50, 51 and over, as some authors prefer. Only the most carefully collected material, by single years, checked and verified wherever possible by clinical inquiry, can serve our need for exact data with regard to the relation between delayed menopause and cancer.

Aside from purely statistical considerations it seems highly desirable to elucidate the whole biological question of the possible role of prolonged estrogenic activity in the development of cancer in the female genital tissues. This requires the consideration of the length of the entire menstrual cycle, so that the age at onset of menstruation should be registered as well as the age at its cessation.

It is a striking and apparently well-established fact that, at least in our temperate climate, menopause at a late age usually occurs in women who started to menstruate at an early age; the reverse condition also being true, that the later the onset the earlier the cessation, as described by E. Novak (14) (15). Individual women will therefore differ considerably in their experience of estrogenic activity, and it may be assumed that these differences in the length of the menstrual cycle have an important bearing on our problem. Thus a woman starting to menstruate at the age of twelve and stopping at fifty-four, with a consequent cycle of forty-two years, may naturally show a quite different biological reaction of the tissues to estrogenic activity from that of the woman starting at sixteen and ending at forty-eight or earlier, with a cycle of estrogenic activity of thirty-two years or less.

Hereditary factors enter into the question of the differences in the range of the menstrual cycle, a phase which has been of interest to the writer for a number of years. E. Petri (16), by means of careful investigation into the records of identical and non-identical twins and of sisters in large families, has already accumulated

much evidence for the determination by genetical factors of at least the onset of the cycle. It is still an open question as to how much hereditary factors, in inter-action with environmental factors, are operative in the varying ranges of the menstrual cycle.

A far more extensive body of material is needed on the actual experience of women with regard to the menstrual cycle than has yet been available and an investigation is now under way which may lead to some understanding of the fact that "breast cancer runs in certain families."

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