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Lactation and Cancer of the Breast

A Summary of an International Study *

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An international collaborative study has been carried out to test the hypothesis that prolonged lactation protects women against cancer of the breast. While pregnancy itself seemed to confer some protection against breast cancer in all areas studied, no consistent differences in duration of lactation were found between breast cancer patients and unaffected women, once the fact that breast cancer patients have fewer pregnancies had been allowed for. Even in areas where some women had lactated for a total of 5 years or more, such women occurred proportionately no less frequently among breast cancer patients than among unaffected women. In the light of this and other recent evidence, it is unlikely that lactation has any protective effect against breast cancer in women, and other explanations must be sought for the remarkable international differences in the frequency of this disease.

The hypothesis that prolonged lactation protects against the development of cancer of the breast is one of the oldest and most enduring hypotheses concerning the etiology of this neoplasm. It could account for several of the major epidemiological features of the disease, including the following:

(1) Most of the countries in which very low rates of breast cancer have been observed are in areas of the world where lactation is customary and frequently prolonged.

(2) Breast cancer risk is inversely associated with high parity, a status that provides increased opportunity for lactation.

(3) There has been a significant increase in breast cancer rates in young women in the USA in recent years (MacMahon, 1958; Feinleib & Garrison, 1969). The fact that this increase has affected successive cohorts of women, rather than particular time periods, suggests that it results from some experience during early life; the decreasing frequency of breast feeding is one possibility.

Moreover, credible mechanisms can be postulated to explain a relationship between long lactation and low breast cancer risk. These include local effects of breast feeding on mammary tissue, as well as hormonal mechanisms dependent on the effect of lactation in changing endocrine patterns.

Recent studies designed to test this hypothesis by comparing the lactation experience of breast cancer patients and controls have given conflicting results. Most of these studies have been undertaken in the USA and in other countries where breast cancer rates are high. Even if studies in the countries of highest risk were consistently negative, their interpretation could be questioned. It is conceivable, for example, that the duration of lactation necessary to

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confer protection against breast cancer is so long that few women in such countries experience it; virtually all women may therefore be at maximum risk with respect to this factor, and the variables that discriminate between affected and unaffected women would be other components of the causal complex.

Therefore, before considering alternative explanations for the international variation in breast cancer rates, it seemed desirable to provide a definitive test of the lactation hypothesis. We considered that such a test should: (1) include areas exhibiting the whole range of observed breast cancer rates, and (2) be based on series of cases known to be representative of all those occurring in the areas rather than on the patients coming to specialized, or otherwise selected, hospitals.

METHOD

The basic design of the study was that of a case-control study, information being obtained by interviewing breast cancer patients and a comparison group of unaffected women. This approach was used in 7 centres, 2 being areas of high breast cancer rates, 2 areas of low rates, and 3 areas where intermediate levels of risk were thought to prevail. The centres were as follows:

High risk : the city of Boston, USA, including certain suburbs, and
the county of Glamorgan, Wales, including the 3 county boroughs of Cardiff, Swansea and Merthyr Tydfil.

Intermediate risk : the city of Greater Athens, Greece,
the Socialist Republic of Slovenia, Yugoslavia, and
the city of São Paulo, Brazil.

Low risk : the prefecture of Tokyo (*Tokyo-to*), Japan, and
the city and county of Taipei, Taiwan.

As judged from available mortality data, these centres represented a 6-fold range of breast cancer rates—from about 26 per 100 000 in the USA to about 4 per 100 000 in Japan and Taiwan.

The features of the study design which were to be common to all centres included the following:

(1) For each centre, a geographically and administratively defined population would be selected.

(2) An attempt would be made to identify all residents of the defined population having a diagnosis of breast cancer established for the first time during a specified period.

(3) Interviews would be attempted with such patients during the period of hospitalization. Patients who left hospital prior to interview would not be interviewed at home, although they would be recorded as incident cases.

(4) As controls, patients under treatment for diseases other than breast cancer were to be interviewed. For each breast cancer patient the 3 eligible patients in the beds closest to the cancer patient at the time of her interview would be selected. Eligibility required also being a resident of the defined population and over 35 years of age (unless the breast cancer patient was under 35 years of age, in which event a specific age match was required). In some instances, 3 eligible controls could not be obtained for each cancer case.

(5) Generally, the same interviewer would interview all members of a " set " consisting of 1 breast cancer patient and 3 controls.

(6) The same interview form, translated as required, would be used in all centres.

(7) At the end of the study, hospital records would be searched for patients who might have been missed during the interviewing period.

(8) A histological specimen would be obtained from each patient and sent to the co-ordinating centre for review by a single pathologist.

(9) Coding, data processing and analysis for all centres would be carried out in the co-ordinating centre. In addition, investigators in each centre would be free to carry out whatever analyses of their own data they wished.

The extent to which these procedures could be followed in the individual centres, as well as the details of the populations surveyed and numbers of cases detected, are described in individual reports (Lowe & MacMahon, 1970; Salber, Trichopoulos & MacMahon, 1969; Valaoras et al., 1969; Yuasa & MacMahon, 1970; and Lin, Chen & MacMahon, Mirra & Cole, Ravnihar, MacMahon & Lindtner, unpublished data). The only major discrepancy bearing on the data to be presented in this paper is that in Tokyo and in São Paulo it proved impossible to identify all cases occurring in the defined population during the study period, and incidence cannot be estimated for these two centres. Nevertheless, the numbers of cases identified in Tokyo and São Paulo, and the variety of institutions from

TABLE 1
TOTAL FEMALE POPULATIONS, NUMBERS OF CASES DETECTED AND PATIENTS INTERVIEWED IN THE CO-OPERATING CENTRES

Centre	Total female population	Study period (month and year inclusive)	No. of breast cancer cases detected	No. of patients interviewed		Breast cancer patients interviewed (%)
				Breast cancer	Comparison patients	
Boston	438 264	1.65–12.66	758	606	1 807	79.9
Glamorgan	629 278	5.65– 4.67	710	619	1 850	87.2
Athens	1 093 269	1.65– 6.67	956	799	2 470	83.6
Slovenia	865 829	10.64–12.67	831	772	2 308	92.9
São Paulo	2 458 556	12.65– 6.68	537	537	1 555	—[a]
Taipei	1 265 984	11.64–10.67	232	213	648	91.8
Tokyo	5 304 661	4.65– 3.67	861	849	2 250	—[a]
Total	12 055 841	—	4 885	4 395	12 888	—

[a] Total incident cases not known.

which they came, give reasonable assurance that the series are representative of all affected women in the two centres.

The numbers of cases detected and patients interviewed are given in Table 1. Altogether, 4885 cases were identified and 4395 patients were interviewed. Nearly 13 000 control patients were also interviewed. The proportion of all new cases identified for which interviews could be arranged was 80% or higher in all centres except the two where total ascertainment of cancer cases was not feasible. In these two areas, on the basis of other information, it is estimated that the patients interviewed comprised about 50% of the total incident cases in Tokyo (Yuasa & MacMahon, 1970) and about 60% of those in São Paulo.

The interviewers were asked to give an opinion on the validity of the information obtained at each interview. In the analyses, interviews rated as unreliable have been excluded. The numbers of such interviews were small (56 cases, 128 controls) and they occurred in similar proportions in the cases and controls. The highest frequencies were in Boston, where 4.3% of the cases and 3.9% of the controls were rated as unreliable.

For 3805 patients (78% of the total of 4885 cases), the diagnosis of cancer was confirmed in histological material sent to the co-ordinating centre. The remaining patients have been included on the basis of local diagnoses alone. In no centre did the proportion of cases without histological confirmation, either local or central, exceed 6% of the total.

The statistical method used was the comparison of observed values in the case series with expected values based on the control series for the corresponding centre. The expected numbers were computed by applying, to the number of cases in each 10-year age-group, the values for the controls in the same age-group, and summing these over all age-groups. All the expected values shown are adjusted for age in this manner. In certain tables, as indicated in the footnotes, the expected values also take account of differences in parity distributions of the compared series. Summary χ^2 tests with 1 degree of freedom, as described by Mantel & Haenszel (1959) and Mantel (1963) were used. In these tests, the expected values are not those shown in the table but are, of course, based on the distributions of the case and control groups combined.

INCIDENCE OF BREAST CANCER

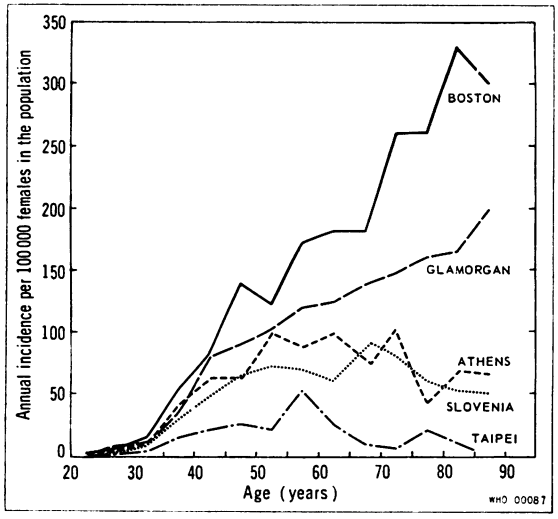
For the five centres in which detection of breast cancer is believed to have been reasonably complete, the average annual incidence rates per 100 000 females in the population, age-adjusted to the standard world population, suggested by Segi (1960) and Doll, Payne & Waterhouse (1966) were as follows:

Centre	*Incidence rate*
Boston	55.0
Glamorgan	38.8
Athens	28.9
Slovenia	24.4
Taipei	9.1

The range between centres—from 55.0 per 100 000 in Boston to 9.1 per 100 000 in Taipei—is similar to that observed in mortality data. As already noted, it is not possible to give a direct estimate of incidence in Tokyo, the other low-risk centre. If the breast cancer incidence rates from the cancer registry in Miyagi Prefecture, Japan (Doll, Payne & Waterhouse, 1966), are adjusted to the same population, a rate of 12.9 per 100 000 is obtained. The actual rate in Tokyo is probably a little higher than this, since Miyagi Prefecture includes both urban and rural areas and breast cancer rates tend to be higher in urban areas.

The accompanying figure shows the age-specific incidence curves for the five centres. These centres illustrate a phenomenon that is also evident in reports from cancer registries (Doll, Payne & Waterhouse, 1966)—namely, that the international differences in breast cancer risk are particularly striking in the older age-groups. In Boston and Glamorgan, rates increase progressively with age throughout life, but in the other centres the rates reach a plateau or decline after middle-age.

AGE-SPECIFIC INCIDENCE RATES OF BREAST CANCER IN 5 STUDY CENTRES, 1965–67



MARITAL STATUS AND PARITY

The analysis of lactation histories is restricted to married women who had at least 1 liveborn child. Single women were excluded because, in most centres, they were not asked whether they had borne children. Within the married group, only women who had a liveborn child had an opportunity to lactate, and it is within this group that the effect of lactation can be separated from other concomitants of pregnancy. However, before turning to this group, the risks of breast cancer in excluded groups have been examined. The relationships involved are generally well known for this disease, although they have not previously been shown to prevail in all the areas included in this study.

Observed and expected numbers of single women among the interviewed patients and estimates of the risks for single women relative to those for women ever married are shown in Table 2. Except in Taipei,

TABLE 2

ESTIMATES OF THE RISK OF BREAST CANCER IN SINGLE WOMEN RELATIVE TO THAT IN WOMEN EVER MARRIED

Centre	No. of cases [a]	No. of cases in single women		Relative risk [b]
		Observed	Expected	
Boston	580	115	89.0	1.36
Glamorgan	611	61	44.3	1.42
Athens	796	81	61.0	1.37
Slovenia	756	122	106.1	1.18
São Paulo	536	73	52.2	1.46
Taipei	210	1	3.4	—
Tokyo	849	66	45.6	1.49

[a] Number of interviewed patients after exclusion of unreliable interviews and patients of unknown marital status.

[b] Risk for the single women relative to a risk of 1.00 for the married women.

where over-all numbers are small and those of single women particularly so, the risks were higher in single than in ever-married women. The excess amounts to between 35% and 50% in all centres except Slovenia, where it was somewhat lower—namely, 18%. It is relevant that in Slovenia 25% of the single women reported having had 1 or more children. This may account for some, though probably not all, of the discrepancy between the data for Slovenia and the other centres.

TABLE 3

ESTIMATES OF THE RISK OF BREAST CANCER IN NON-PAROUS MARRIED WOMEN RELATIVE TO THAT IN PAROUS MARRIED WOMEN

Centre	No. of married patients [a]	No. of patients non-parous [b]		Relative risk [c]
		Observed	Expected	
Boston	463	88	68.0	1.36
Glamorgan	550	100	65.3	1.65
Athens	713	133	106.1	1.31
Slovenia	634	63	55.9	1.14
São Paulo	459	49	41.8	1.19
Taipei	209	32	12.9	2.75
Tokyo	783	158	109.3	1.56

[a] Cases of unknown parity excluded.

[b] "Non-parous" defined as never having borne a full-term child, liveborn or stillborn.

[c] Risk for the non-parous married women relative to a risk of 1.00 for the parous married women.

TABLE 4

OBSERVED AND EXPECTED NUMBERS OF STILLBIRTHS AMONG THE CHILDREN OF THE BREAST CANCER PATIENTS; EVER-MARRIED WOMEN ONLY

Centre	No. of women	No. of full-term births	No. of stillbirths		χ^2 [b]
			Observed	Expected [a]	
Boston	465	1 069	37	35.3	0.1
Glamorgan	550	1 189	74	57.1	*3.8*
Athens	715	1 564	65	46.5	*4.4*
Slovenia	634	1 809	51	55.8	0.3
São Paulo	459	1 748	49	46.2	0.0
Taipei	209	758	19	16.5	0.0
Tokyo	784	1 766	77	73.7	0.1

[a] Expected values based on the stillbirth rates in the appropriate control group, with adjustment for age at the time of interview.

[b] χ^2 values are Mantel–Haenszel summary χ^2 tests with 1 degree of freedom. For $P = 0.05$, $\chi^2 = 3.84$. Values equal to or greater than 3.84 are in italics.

Among the ever-married women, observed and expected numbers who never delivered a full-term child are given in Table 3. In all centres, risks were higher for the non-parous than for the parous women. Except in São Paulo, where the risk for single women relative to that for married women (1.46) was appreciably greater than that for non-parous relative to parous women (1.19), the relative risks for the individual centres given in Tables 2 and 3 are quite similar, suggesting that most, or perhaps all, of the excess risk of the single women can be attributed to their non-parity rather than to some other aspect of their marital status.

In two centres, there was a statistically significant excess of stillbirths among the children of breast cancer patients (Table 4). While this relationship was not found in the other centres, it seemed preferable to omit women who had only stillborn children from the analysis of lactation, and they have in fact been excluded. It is true that women who have stillborn children usually do not lactate. However, even if a high stillbirth rate were a characteristic of women who develop breast cancer, mechanisms other than lack of opportunity for lactation can be postulated to explain such a relationship. Therefore, the inclusion of stillbirths in a test of the lactation hypothesis would, if they occurred in excess in sufficient numbers in one or the other series, necessarily introduce a difference in lactation patterns. In fact, the number of such women is too small to influence the data appreciably, and the question of their inclusion or exclusion is somewhat academic.

LACTATION HISTORY

The numbers of married women who had at least 1 liveborn child, and a summary of their lactation experience, are given in Table 5. Four measures of lactation were examined:

(1) The number of women who had 1 or more liveborn children but who had never lactated.

(2) The number of liveborn children who were not breast-fed.

(3) The mean duration of lactation for children who were breast-fed.

(4) The number of women whose total lactation time was unusually long.

With respect to (4), lactation practices varied substantially between centres, and in order to obtain a group that was unusual for the centre, but yet large enough for meaningful analysis, it was necessary to adopt different values to define an "unusually long" total lactation experience. The use of "more than 5 years (60 months)" in São Paulo, Taipei and Tokyo and of "more than 2 years (24 months)"

TABLE 5

SUMMARY OF FINDINGS WITH RESPECT TO SELECTED MEASURES OF LACTATION EXPERIENCE

	Boston	Glamorgan	Athens	Slovenia	São Paulo	Taipei	Tokyo
No. of cases [a]	375	445	574	564	410	410	610
No. of controls [a]	1 259	1 479	1 893	1 773	1 253	586	1 817
No. who never lactated:							
Observed [b]	89	99	24	31	20	17	36
Expected	99.1	108.6	24.4	22.3	17.5	17.6	38.2
No. who lactated for long periods: [c]							
Observed [b]	49	58	231	166	104	50	127
Expected	46.1	60.6	246.3	156.2	113.0	57.5	130.3
No. of children: [d]							
of cases	1 034	1 115	1 489	1 759	1 699	739	1 690
of controls	3 980	4 113	5 271	5 597	5 957	2 547	6 050
No. not breast fed:							
Observed [b]	*384*	*340*	90	*133*	121	104	130
Expected	418.2	378.4	79.2	107.5	129.8	111.4	120.6
Mean duration of breast feeding: [e]							
Observed [b]	6.2	6.5	11.6	7.4	12.3	13.2	15.2
Expected	5.7	6.6	12.3	7.2	12.0	14.6	15.2

[a] Married women with at least 1 liveborn child.

[b] Observed values are those in the breast cancer patients. Expected values are based on the control series adjusted to the age and parity distribution of the patients. The observed values in italics differ significantly ($P < 0.05$) from the expected.

[c] In São Paulo, Taipei and Tokyo this is the number who nursed for more than 5 years (60 months). In the other centres it is the number who nursed for more than 2 years (24 months).

[d] Liveborn children born to breast cancer patients or controls.

[e] Mean duration of lactation (months) among children who were breast fed.

in the other centres identified approximately 25% of the total group, rather less in some centres (13% in Boston and Glamorgan) and rather more in others (40% in Athens).

For each of these measures, the observed numbers in the breast cancer series were compared with expected values computed from rates in the corresponding control series specific for age (in decades) and parity (single parities up to 5 or more) simultaneously.

There are 28 comparisons of observed and expected values in the table. In 13 of these 28 comparisons the difference between observed and expected was in the direction favouring a protective effect of lactation (i.e., less lactation in the cases than expected), and in 14 instances the difference was in the opposite direction. In 1 instance the observed and expected values were identical. Summary χ^2 values were computed for all 28 comparisons. In 3 instances there was a statistically significant difference between observed and expected values—1 was in the direction favouring the hypothesis and 2 were contrary. However, all three statistically significant differences occurred in measure (2). An objection may be raised to the application of the significance test to this particular measure, namely, that the probabilities of each of the included children being breast-fed are not independent since there is a tendency for all the children of a given mother to be treated similarly. The χ^2 tests, which assume independence, therefore underestimate the probabilities of the differences being due to chance.

Effect of socio-economic status

After parity and age, socio-economic status is perhaps the variable most likely to confound an analysis of lactation and breast cancer risk, since it has been shown on many occasions to be associated with both characteristics. The measure of socio-economic status most clearly related to breast cancer risk in our data was duration of the patient's schooling. There was indeed a strong inverse relationship between duration of schooling and duration of lactation in the control series of each centre (Table 6).

TABLE 6

PERCENTAGE OF MARRIED CONTROL PATIENTS WITH AT LEAST 1 LIVEBORN CHILD WHO LACTATED FOR RELATIVELY LONG PERIODS,[a] BY YEARS OF SCHOOLING

Centre	Years of schooling [b]					Total
	None	<8	8–11	12–15	⩾16	
Boston	—	28.8	13.0	4.4	6.7	11.1
	(24)	(128)	(389)	(627)	(95)	(1 269)
Glamorgan	—	14.8	12.7	5.8	—	12.7
	(3)	(37)	(1 368)	(71)	(12)	(1 493)
Athens	50.5	44.5	43.0	26.4	—	44.5
	(373)	(1 169)	(190)	(163)	(18)	(1 914)
Slovenia	—	29.4	22.9	27.7	—	28.2
	(13)	(1 162)	(438)	(149)	(9)	(1 781)
São Paulo	40.4	29.7	8.3	1.4	—	32.7
	(406)	(728)	(95)	(26)	(6)	(1 261)
Taipei	43.2	34.7	21.6	18.5	8.7	33.2
	(160)	(232)	(82)	(76)	(38)	(588)
Tokyo	—	39.6	25.4	7.8	—	28.1
	(18)	(420)	(1 164)	(215)	(17)	(1 836)

[a] In São Paulo, Taipei and Tokyo, this is the percentage who lactated for more than 5 years (60 months). In the other centres it is the percentage who lactated for more than 2 years (24 months). The percentages are adjusted to allow for differences in parity distribution between educational classes within centres but not between centres.

[b] Values in parentheses are the numbers on which the estimates are based. No estimates are given for cells containing less than 25 women.

This relationship was in the direction contrary to that which would lead us to overlook a true protective effect of lactation against breast cancer. That is to say, breast cancer tended to occur more frequently in the higher socio-economic groups and, since women in such groups lactate less, it might have been expected that the patients would have had shorter total periods of lactation on this basis alone.

Indeed, the relationships in Table 6 are so strong that we must inquire whether, by neglecting socio-economic status (Table 5), an association of lactation with *increased* breast cancer risk has been overlooked. In Table 7, the observed and expected values from the bottom row of Table 5 are shown, together with the expected values computed with adjustments for age, parity and duration of schooling. The effect of the additional adjustments is trivial, and in 5 of the 7 centres serves only to move the expected values somewhat closer to the observed values.

TABLE 7

OBSERVED NUMBERS OF BREAST CANCER PATIENTS WHO BREAST FED AT LEAST 1 CHILD AND WHO LACTATED FOR RELATIVELY LONG PERIODS,[a] AND EXPECTED VALUES ADJUSTED FOR AGE, PARITY AND DURATION OF SCHOOLING

Centre	Observed	Expected	
		A [b]	B [c]
Boston	49	46.1	45.2
Glamorgan	58	60.6	60.2
Athens	231	246.3	239.6
Slovenia	166	156.2	157.2
São Paulo	104	113.0	110.5
Taipei	50	57.5	59.2
Tokyo	127	130.3	128.5

[a] Same criteria as in Tables 5 and 6.

[b] Expected with adjustment for age and parity, as in Table 5.

[c] Expected with adjustment for age, parity and duration of schooling.

Individual age- and parity-groups

A previous report from Japan has suggested that lactation may be a significant protective factor in

breast cancers developing in women over 40 years of age, but not in those occurring in younger women (Kamoi, 1960). It is necessary therefore to examine characteristics of the lactation experience in individual age-groups. Examination of individual parities is also suggested by the observation, to be reported subsequently,[1] that breast cancer risk is strongly associated with the age at which a woman has her first pregnancy. In the more detailed reports from the individual centres analyses of lactation characteristics for separate age- and parity-groups have therefore been shown. No significant or consistent differences between cases and controls were found within any classification by parity or age at diagnosis of the cancer.

DISCUSSION

The hypothesis that lactation reduces breast cancer risk has been the subject of more polemics than studies. The support to be found in the literature is not as strong as the popularity of the hypothesis would suggest. In early studies, Lane-Claypon (1926) and Wainwright (1931) found both absence of lactation and very prolonged lactation to be more frequent in breast cancer patients than in controls. In neither study was the selection of cases and controls satisfactory by present-day standards. MacDonald (1942) came to a most definite conclusion in support of a protective effect of lactation, but the comparison on which the conclusion was based is quite indefensible. More recently, two studies in the USA (Levin et al., 1964; Kaplan & Acheson, 1966), one in France (Schwarz, Denoix & Rouquette, 1958), two in Japan (Segi et al., 1957; Kamoi, 1960) and one involving several areas (Wynder, Bross & Hirayama, 1960) have indicated either less frequent or less prolonged lactation among breast cancer patients than among controls. However, the differences in all these studies have been quite small, and in none have the interrelationships of parity, socio-economic status and nursing been adequately separated. Two studies in the USA (MacMahon & Feinleib, 1960; Shapiro et al., 1968), and a small but very carefully controlled study in Israel (Abramson, 1966), have not revealed any appreciable differences in the lactation experience of breast cancer patients and unaffected women.

It is noteworthy that only one of these past studies (Shapiro et al., 1968) is based on all cases occurring in a defined population. The opportunities for the introduction of differences between patients and controls in socio-economic status, in addition to the evident tendency of breast cancer to affect higher economic groups disproportionately, are therefore manifold. The relatively small effect of adjustment for this variable in the present study does not exclude the existence of more important confounding effects in other studies using different methods of case or control selection. Furthermore, few past studies have adequately separated the effect of childbearing from that of breast feeding. Thus, the use of the measure "mean duration of lactation per child" does not adequately allow for parity differences between patients and controls since women of high parity tend to have a long lactation, quite independently of their greater opportunity for lactation. For example, in the Boston control series in the present study, the mean duration of lactation per child breast-fed was 3.0 months for women of parity 1 and 6.4 months for women of parity 5 or more (Salber, Trichopoulos & MacMahon, 1969). Adding to these difficulties the small numbers involved in some previous studies, it is not surprising that findings have been inconsistent.

It is believed that the data reported in this paper compare favourably with those previously available with respect to biases introduced in the selection of the material. In addition, the large numbers of cases included, even in areas of low breast cancer risk, such as Japan, have allowed more comprehensive analyses to be made of the role of factors such as socio-economic status, parity and age. However, two methodological aspects of the present study deserve discussion. They are the use of other hospital patients as the source of the control groups and the reliance on women's memories regarding the duration of their lactation.

Other hospital patients were used in this study because no other control group could conveniently be assembled in all centres. Many investigations for which a hospital control group might be unsuitable can be visualized. Intuitively, there seems little reason to suppose that the study of lactation may be among these, particularly if, in the analysis, allowance is made for the distributions of the case and control series by age, parity and socio-economic status. However, to assess the validity of this supposition, a second control group was assembled in Boston from town census records. Findings with respect to lactation in this second control group drawn from the general population did not differ

[1] MacMahon, B., Cole, P., Lin, T. M., Lowe, C. R., Mirra, A. P., Ravnihar, B., Salber, E. J., Valaoras, V. G. & Yuasa, S., *Age at first birth and breast cancer risk* (in preparation).

significantly, or consistently, from either the breast cancer cases or the hospital control group (Salber, Trichopoulos & MacMahon, 1969).

Regarding the reliability of lactation histories, it was possible, in some centres, to re-interview a sample of women 3–12 months after the original interview. The numbers of patients re-interviewed were: Boston controls 44, Glamorgan controls 49, Slovenia cases 48 and Taiwan cases and controls 29. There were a number of discrepancies in the information given at the two interviews. However, these were not of the magnitude, nor did they carry sufficient bias, to influence substantially the conclusions presented. For example, the two most critical measures of our analyses are the proportion of women who never lactated, and the proportion who lactated for a relatively long period (as defined in Table 5). With respect to the former, among the 170 re-interviewed women, 51 were originally coded as having never lactated and 5 of these would not have been so coded on the basis of the re-interview; 3 women not originally assigned to this class would have been so coded on the basis of re-interview. Regarding the number who lactated for long periods, 34 of the 170 were originally coded to this class; 3 of these would not have been so coded on the re-interview, and there were 3 not so coded originally who would have been coded in this category on the re-interview. Of course, these data reflect on the reliability, rather than on the validity, of the lactation histories. However, the strong relationships with socio-economic status noted in Table 6 do suggest that real differences between women with respect to lactation experience were revealed by the interviews.

In short, while both the use of a hospital control group and the reliance on patients' memories have no doubt introduced inaccuracies and inefficiences into our material, it is not thought that these can have been sufficient to lead to any appreciable excess or deficiency of lactation in the case series being overlooked.

The failure to confirm the hypothesis of the protective effect of lactation in these centres representing such a wide range of breast cancer risk, and including areas where appreciable numbers of women have very long lactation experiences, indicates that other hypotheses must be developed to account for the observed international differences in breast cancer rates.

The finding also has relevance to at least one hypothesis concerning the mechanism underlying the relationship between ovarian function and breast carcinogenesis. It has been suggested that it is the cyclic nature of ovarian activity that is particularly significant in breast cancer etiology, and that circumstances which interrupt cyclic ovarian activity reduce breast cancer risk (Wynder, Bross & Hirayama, 1960; Levin et al., 1964; Feinleib, 1968). In several of the centres in this study, the mean duration of lactation per child exceeded the usual duration of pregnancy (Table 5), and in such areas the interruption of cyclic ovarian activity associated with lactation was presumably as long as that associated with pregnancy. Since in these centres lactation was not, but pregnancy was, associated with decreased breast cancer risk, the cyclic activity hypothesis seems an inadequate explanation of the mechanism of reduced risk associated with pregnancy.

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RÉSUMÉ

LACTATION ET CANCER DU SEIN: COMPTE RENDU SUCCINCT D'UNE ÉTUDE INTERNATIONALE

On a procédé parmi sept groupes de population à une enquête sur les antécédents en matière de lactation de malades atteintes de cancer du sein et de femmes indemnes de cette affection. Deux des groupes ont été choisis dans des régions où le risque de cancer du sein est élevé (Boston, Etats-Unis d'Amérique, et Glamorgan, Pays

de Galles), deux dans des régions où ce risque est faible (Taïpeh, Taïwan, et Tokyo, Japon) et trois dans des régions où les taux d'incidence de l'affection sont de valeur intermédiaire (Athènes, Grèce; Slovénie, Yougoslavie, et São Paulo, Brésil). On s'est efforcé, dans chacun de ces échantillons de population, d'interroger toutes les femmes atteintes d'un cancer du sein diagnostiqué pour la première fois au cours de l'enquête. Aux fins de comparaison, on a également recueilli, pour chaque cas de cancer du sein, les antécédents de trois malades, d'âge correspondant, hospitalisées pour d'autres raisons.

Dans cinq des centres d'étude, les investigations ont pu être menées avec une rigueur suffisante, les enquêteurs ayant réussi à s'entretenir avec plus de 80% des patientes atteintes de cancer du sein. Les taux d'incidence annuelle de la maladie atteignaient, par 100 000 femmes, 55,0 à Boston, 38,8 à Glamorgan, 28,9 à Athènes, 24,4 en Slovénie et 9,1 à Taïpeh. On estime que, dans les autres secteurs, l'enquête a porté sur environ 50% (Tokyo) et 70% (São Paulo) des nouveaux cas. Au total, quelque 4400 malades atteintes de cancer du sein et près de 13 000 femmes souffrant d'autres affections ont été interrogées sur leurs antécédents en matière de lactation.

Ainsi qu'il était prévu, on a relevé une plus forte proportion de femmes célibataires et de femmes mariées nullipares parmi les patientes atteintes de cancer du sein que parmi les malades témoins. Cependant, chez les mères d'un ou plusieurs enfants vivants, et compte tenu des variations relatives à l'âge, au nombre d'accouchements et au niveau socio-économique, on ne notait aucune différence nette sous le rapport de la durée de la lactation — appréciée selon divers critères — entre les femmes atteintes de cancer du sein et les autres malades. On a procédé chez les femmes atteintes de cancer du sein à 28 comparaisons distinctes portant sur la durée de la lactation telle qu'elle était observée et sur sa durée escomptée, évaluée d'après les chiffres relevés chez les malades témoins présentant des caractéristiques identiques en ce qui concerne l'âge et le nombre d'accouchements. Dans 13 de ces comparaisons, la différence entre la valeur observée et la valeur escomptée plaidait en faveur d'un rôle protecteur de la lactation; dans 14 autres, la discordance donnait à penser que la lactation a un effet favorisant sur l'apparition du cancer du sein; une comparaison enfin montrait une concordance entre la valeur observée et la valeur escomptée.

La conclusion tirée de la présente étude est que la lactation, même prolongée pendant de longues périodes, n'a aucune influence sur le risque de cancer du sein auquel est exposée une femme. D'autres mécanismes sont en jeu qu'il faut élucider si l'on veut expliquer les variations considérables de l'incidence de l'affection dans différents pays. Les constatations faites au cours de cette enquête semblent par ailleurs infirmer la théorie selon laquelle le risque de cancer du sein serait dépendant de la durée des phases d'activité cyclique de l'ovaire.

REFERENCES

Abramson, J. H. (1966) *Israel J. med. Sci.*, **2**, 457-464

Doll, R., Payne, P. & Waterhouse, J. (1966) *Cancer incidence in five continents*, New York, Springer

Feinleib, M. (1968) *J. nat. Cancer Inst.*, **41**, 315-329

Feinleib, M. & Garrison, R. J. (1969) *Cancer*, **24**, 1109-1116

Kamoi, M. (1960) *Tohoku J. exp. Med.*, **72**, 59-65

Kaplan, S. D. & Acheson, R. M. (1966) *J. chron. Dis.*, **19**, 1221-1230

Lane-Claypon, J. E. (1926) *A further report on cancer of the breast with special reference to its associated antecedent conditions.* In: *Report on Public Health and Medical Subjects No. 32*, London, H.M. Stationery Office

Levin, M. L., Sheehe, P. R., Graham, S. & Glidewell, O. (1964) *Amer. J. publ. Hlth*, **54**, 580-587

Lowe, C. R. & MacMahon, B. (1970) *Lancet*, **1**, 153-157

MacDonald, I. (1942) *Surg. Gynec. Obstet.*, **74**, 75-82

MacMahon, B. (1958) *Cancer*, **11**, 250-254

MacMahon, B. & Feinleib, M. (1960) *J. nat. Cancer Inst.*, **24**, 733-753

Mantel, N. (1963) *J. Amer. statist. Ass.*, **58**, 690-700

Mantel, N. & Haenszel, W. (1959) *J. nat. Cancer Inst.*, **22**, 719-748

Salber, E. J., Trichopoulos, D. & MacMahon, B. (1969) *J. nat. Cancer Inst.*, **43**, 1013-1024

Schwartz, D., Denoix, P. F. & Rouquette, C. (1958) *Bull. Ass. franç. Cancer*, **45**, 476-493

Segi, M. (1960) *Cancer mortality for selected sites in 24 countries (1950–57)* Sendai, Department of Public Health, Tohoku University School of Medicine

Segi, M., Fukushima, I., Fujisaku, S., Kurihara, M., Saito, S., Asano, K. & Kamoi, M. (1957) *Gann*, **48** suppl., pp. 1-63

Shapiro, S., Strax, P., Venet, L. & Fink, R. (1968) *Amer. J. publ. Hlth*, **58**, 820-835

Valaoras, V. G., MacMahon, B., Trichopoulos, D. & Polychronopoulou, A. (1969) *Int. J. Cancer*, **4**, 350-363

Wainwright, J. M. (1931) *Amer. J. Cancer*, **15**, 2610-2645

Wynder, E. L., Bross, I. J. & Hirayama, T. (1960) *Cancer*, **13**, 559-601

Yuasa, S. & MacMahon, B. (1970) *Bull. Wld Hlth Org.*, **42**, 195-204