Based on studies under way since 1957, findings are reported that indicate the risk of breast cancer increases with extended menstrual activity. With respect to lactation the situation may be more complex, the risk of breast cancer declining for lactation more than 17 months, but not for shorter periods. Differences in incidence in certain countries may be due to varying menstrual and lactating activities.

LACTATION AND MENSTRUAL FUNCTION AS RELATED TO CANCER OF THE BREAST

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THE purpose of this paper is to present a brief summary of the findings to date in the research program on the epidemiology of breast cancer which has been under way at Roswell Park Memorial Institute since 1957. The objective of this program has been to test hypotheses current in the literature, particularly those relating breast cancer to lactation and menstrual activity. Interest in the nursing hypothesis was generated most importantly with the publication in 1926 of Janet Lane-Claypon's work showing a larger percentage of the children of control cases to have been nursed than was true with children of breast cancer patients.[1] Subsequently, replications by Wainwright and Lewison resulted in similar findings, but those by Lewison in a second study, by Taylor, and most recently, MacMahon and Feinleib failed to corroborate Lane-Claypon's result.[2-6] In addition, the observation of a change in the pattern of age specific incidence of breast cancer in postmenopausal as compared to premenopausal years, together with the finding of other related factors, such as fertility, stimulated interest in examining menstrual activity in more detail than had been done previously.[7,8]

As a result of our interest in these findings, studies of two series of patients at Roswell Park Memorial Institute were undertaken. In addition, a study was begun of all cases in Buffalo and Kenmore in 1957-1962, as compared to random sample controls from these communities. Data collection from the community studies will conclude shortly. The present discussion relates to our studies on hospital patients at Roswell Park Memorial Institute.

Routinely, all patients entering Roswell Park Memorial Institute on either an in- or outpatient basis are interviewed regarding characteristics which might be related to the epidemiology of a number of types of cancer. Included among these are fertility, birth weight of children, miscarriages, stillbirths, nursing history, menstrual history, radiation exposure, and the like. Analysis of interview data obtained on the series of breast cancer patients who entered the hospital between April 17, 1955, and April 17, 1957, revealed a number of differences when compared to data obtained from con-

Table 1—Factors Associated with Increased or Decreased Risk of Breast Cancer

Factor	Risk Compared to General Population
Artificial menopause	0.50
Nursed 36 months or more	0.46
Never married	1.07
Married, never pregnant	1.08
Married more than once, never pregnant	1.42
Married after age 25; one or more live births	1.47
First pregnancy after age 25	1.36
Married, pregnant, live births, never nursed	1.24
Nursed less than 36 months	1.21

trols. Patients utilized as controls consisted of those diagnosed to be free of neoplastic disease as well as free of any disease of the reproductive organs or of the breast.

Table 1 presents data on certain of the differences observed in terms of indicated risk of breast cancer for persons with a trait relative to that for persons in the general population. The risk of breast cancer is less for persons who have had artificial menopause or who have nursed longer than 36 months in their lifetimes. Risk is increased for women who have never married, who have never been pregnant, who have had their pregnancies relatively late in life, or who have never nursed. The relative risks range from 0.46 for those lactating more than 36 months, and 0.50 for those with an artificial menopause, to 1.24 for those who had live births but never nursed, and 1.47 for those married after age 25. It is apparent that the differentials in these relative risks are not large.

At about the time these findings were developed, MacMahon published data showing no significant relationship between nursing and breast cancer. The difference between MacMahon's and our result might have been accounted for by many factors, among them differences in the series studied. Thus, MacMahon's breast cancer series was from a clinic population of probably low socioeconomic status, whereas the Roswell Park series from Buffalo and Kenmore is distributed into socioeconomic categories in almost an identical way as a random sample of that population. Inasmuch as high socioeconomic status may be related to breast cancer, the differences in the New York City and Buffalo data possibly might be explained on this basis. Also, MacMahon's analysis was conducted by matching cases with controls, whereas the Roswell Park series was studied in toto with adjustment only for age, according to the direct method. To explore the latter possibility, a replication of the MacMahon study was carried out on our series through matching cases and controls.

For each case, a control matched for age within ten-year-age groups, for race, religion, marital status, parity, and native or foreign birth was chosen at random from the series of females with nonneoplastic, nonreproductive diseases. The matched results (Table 2) showed that the breast cancer cases nursed an average of 17.8 months (S.E. 1.43) whereas the controls nursed 22.2 months

Table 2—Results of Matched Study of Breast Cancer Cases and Controls

	Breast Cancer	Controls
Mean months nursed	17.8 ± 1.43	22.2 ± 1.18
Mean years menstruated	29.1 ± 0.40	27.6 ± 0.48
Mean age at natural menopause	49.7 ± 0.28	47.2 ± 0.39
Mean age at artificial menopause	41.6 ± 1.04	40.4 ± 0.92

Table 3—Paired Breast Cancer Data According to Selected Categories of Absolute Case-Control Differences in Menstrual Years (1955 to 1957 Series)

Paired Difference (Menstrual Years)	Number of Pairs		Odds	Natural Log Odds
	Obverse	Inverse		
1.0 to 1.1	7	8	0.88	−0.13
4.7 to 5.2	9	6	1.46	0.38
9.0 to 10.7	9	6	1.46	0.38
14.0 to 16.3	11	4	2.56	0.94

(S.E. 1.18). Similarly, the mean number of years spent menstruating for cases was 29.1 (S.E. 0.40) and for controls 27.6 (S.E. 0.48). Inasmuch as these cases were matched on parity, and as menarche occurred at similar ages for cases and controls, the difference in menstrual years is mainly determined by differences in age at attaining menopause. Analysis of age at natural menopause for cases was shown to be 49.7 (S.E. 0.28) and that for controls 47.2 (S.E. 0.39). Cases similarly had a later age at artificial menopause than controls.

It was surmised that a more rigorous test of the possible relationship of lactation and menstruation to breast cancer would be one which measured dose-response. Thus, on the basis of the past findings, it was hypothesized that with each increase in years of menstruation there would be a concomitant increase in risk of breast cancer. Conversely, it was hypothesized that with each increase in months spent lactating there would be a decrease in the risk of breast cancer. Through the use of dynamic risk analysis, a method which is described in detail elsewhere, a test of these hypotheses was made.[9] Each appeared to be upheld. It was felt necessary, in addition, to test the hypotheses on a second set of data. For this reason, data on these same variables which had been collected through interviews of a second series of patients entering the institute between April 18, 1957, and December 1, 1959, were subjected to the same kind of analysis. In this second analysis, cases and controls were matched as before, except for a closer match on age and pregnancy history. Cases under 60 at diagnosis were matched within two years, and those over, within four years. In addition, matching was on number of months pregnant rather than on parity as in the first study.

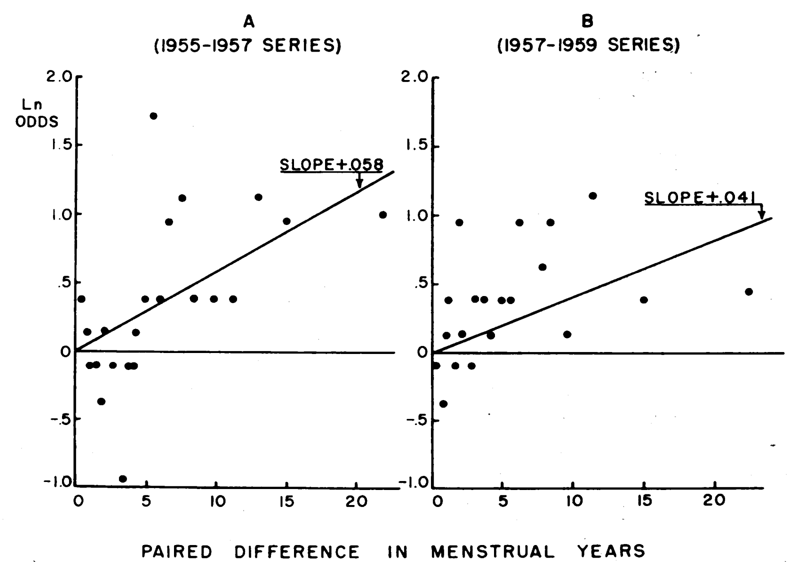
The focus of both the first and second studies was on total menstrual years and total lactating months for cases and controls. The first column of Table 3 shows selected categories of paired case-control differences in menstrual years. For illustrative purposes, only four categories are shown. It is revealed that in the first category—1.0 to 1.1 menstrual years difference—seven pairs showed an excess for the case (seven obverse pairs) and eight showed an excess for the control (eight inverse pairs). In the first study, the total obverse pairs was 194 as compared to 137 inverse. The second study showed similar results. The ratio of the number of obverse pairs plus one-half to the number of inverse plus one-half gives the estimated odds in favor of an obverse pair in each category. It is interesting that as the size of the difference in menstrual years between cases and controls increases, the odds in favor of an obverse pair increases.

In Figure 1 natural log odds for every category are plotted against paired differences in menstrual years for each study. Weighted least squares lines of proportionality have been drawn from the origin. In the first study, the slope is +0.58. It is significantly different from zero ($P<0.0001$). The slope in the second study is +0.041, also highly significant ($P<0.002$). The observed log odds appear to fluctuate radically about the lines of proportionality, but in fact the degree of fluctuation is less than would be expected by chance alone, and no clear pattern of fluctuation is in evidence. The proportionality constants of +0.058 and +0.041 are not significantly different from each other, and this permits the combination of the two slopes into a single estimate of the proportionality constant, +0.049. The 95 per cent confidence interval for the true proportionality constant is from +0.030 to +0.068. This is interpreted to mean that the risk of breast cancer during menstrual years increases 4.9 per cent faster than during postmenopausal years.

Unless there is some systematic tendency within each age class for the hospital to favor the selection of breast cancer cases with long menstrual histories, and not to favor controls with long menstrual histories, the results of these studies are quite striking. First, the structure of the working hypothesis, which is in harmony with previous studies of breast cancer, is supported by the data from both of our hospital studies. Second, the initial observation of a significant slope constant, +0.058, is confirmed subsequently by an observed +0.041.

Table 4 shows the results of a similar kind of analysis for the risk obtaining for each month of lactation, adjusted for the effect of menstruating, which our own and other studies show to be significantly related to breast cancer. In this analysis, pairs of cases are arranged according to categories of case-control difference in lactation history, ranging from the one extreme category of −71 to −26 months to the other at +19 to +39 months. Four categories, selected at approximately equal intervals along

Figure 1—Natural Log Odds* versus Paired Differences in Menstrual Years



*Each plotted point is based on 15 matched case-control pairs.

Table 4—Paired Breast Cancer Data According to Selected Categories of Case-Control Differences in Lactating Months (1955 to 1957 Series)

Difference in Lactating Months	Number of Pairs		Natural Log Odds		
	Obverse*	Inverse†	Observed	Expected	Difference
−71 to −26	11	4	0.94	0.42	0.52
−25 to −17	10	4	0.85	0.52	0.33
0	30	22	0.31	0.28	0.03
19 to 39	9	6	0.38	0.48	−0.10

* Obverse pair: Case menstrual years greater than control.
† Inverse pair: Control menstrual years greater than case.

the continuum are presented in the table. The observed natural log odds are obtained by the ratio of obverse to inverse pairs in terms of menstrual experience, as before. The expected risk, based on the results already obtained in the preceding analysis, is presented to indicate the risk due solely to differences in menstrual histories. Assuming that in the general population there is no association of total menstrual with total lactation experience, the difference between expected and observed is that relating to lactation. It will be noted that as the difference in months of lactation increases, the difference between observed and expected decreases.

Figure 2 shows weighted least squares regression lines drawn for each study. There is no significant variation about the line in either study. The negative slope (−0.0115 per month) in the first study is not significant at the 0.05 level, but the strong negative slope (−0.036 per month) in the second study is highly significant ($P<0.001$). A combined estimate of slope is in order because the two slopes do not differ significantly from each other. The combined estimate is −0.0207 per month, or, to use an annual basis, −0.248 per year. The 95 per cent confidence interval ranges from −0.090 to −0.406 per year.

This indicates that the effect of lactation may be of special significance in retarding the risk of breast cancer. Recall that risk of breast cancer was found to accelerate faster during menstrual years than postmenopausal years, the differential rate of change in risk being 4.9 per cent per year. The present analysis indicates that risk of breast cancer accelerates faster during postmenopausal years than during lactating phases. The differential rate of change is estimated at 24.8 per cent per year, more than five times the difference between menstrual and postmenopausal slopes.

However, the validity of this estimate of the effect of lactation may be rightly questioned because of the assumption of no association between lactation and menstrual histories in the general population. Therefore, we have carried out another analysis which does not require such an assumption. Admissions for 1955 to 1959 were pooled for this study in order to yield as many pairs as possible. Controls were matched with cases, as before, on age, race, native-foreign birth, religion, marital status, and months pregnant, but in addition they were matched on age at menopause within three years. Because the pairs were matched on age at diagnosis as well as age at menopause, the number of postmenopausal years for both cases and controls tended to be equal. The number of pre-menarchal years tended to be equal because of little variation in age at menarche. Also months pregnant tended to be equal because of the match. Consequently, only lactation history and menstrual history were left free to vary. In this way, the difference between rates for lactation versus menstrual phases could be estimated with no further assumptions needed.

Contrary to expectations, the data did not reveal a steady fall in log relative risk as the difference in lactating months increased. As shown in Figure 3, log relative risk goes up significantly from one to about 17 months. From that point on, the log relative risk declines significantly, as would be predicted by hypothesis. At 17 months, the moving average reaches a relative risk of 1.7. Relative risk falls back to unity at about 25 months and continues down to 0.50 at 41 months. The 0.50 estimated at 41 months compares well with the previously estimated 0.46 for women who nursed 36 months or more. The concave pattern of log relative risk in Figure 3 indicates that the influence of lactation may be more complex than was supposed originally. The rate differential for lactation can no longer be expressed, as before, in terms of a single slope of a line emanating from the origin. Rather, the slope of a line from the origin to a point on the moving average will vary with the difference in lactating months. For example, the slope is +0.35 for a difference of 17 months; for 25 months, it is zero; and for 41 months the slope has declined to −0.21. Thus, over a 41 month interval, the differential rate of change in risk (i.e., the slope) is estimated at an average of −21 per cent per year.

The implications of the research discussed to this point are that, viewed in cross-sectional retrospective analysis, a long nursing history and a short menstrual history may carry some diminished risk of breast cancer. On the other hand, an intermediate history of about 17 months of lactation may carry some excess risk of breast cancer. Now if menstrual and lactation activity may be said to be related to mammary cancer etiology, it is possible that differences in such activities may account for dif-

Figure 2—Deviation of Observed from Expected Natural Log Odds as Related to Paired Differences in Lactating Months

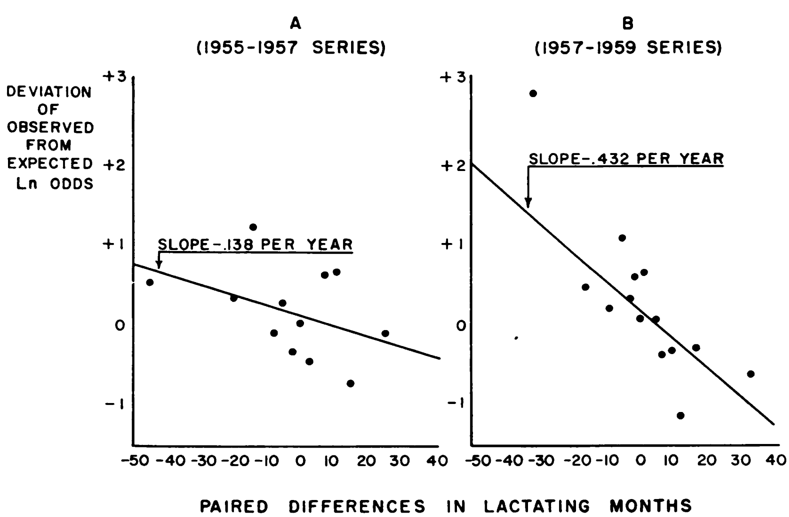
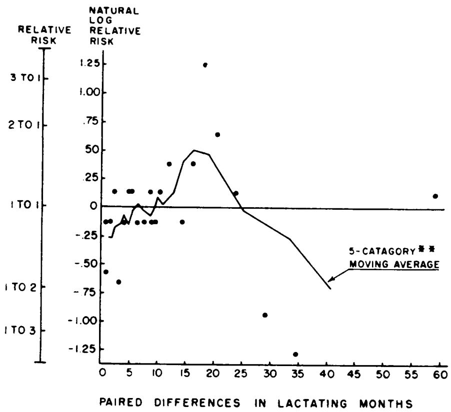


Figure 3—Relative Risk* of Breast Cancer as Related to Paired Difference in Lactating Months (1955-1959 Series)



* Each plotted point is based on 15 matched case-control pairs.

**First and last points of moving average are based on 3 categories.

ferences in incidence of this disease in certain countries. The United States has a conspicuously high rate of incidence for mammary cancer, while Japan has a very low rate. Two investigators in particular have examined the epidemiology of the disease in Japan.[10-13] A comparison of their findings regarding nursing, menstrual activity, and other factors relating to childbirth, with those of the controls at Roswell Park Memorial Institute suggests that Japan does indeed have the nursing and menstrual characteristics predicted on the basis of their low incidence. This, of course, is based on the possibly tenuous assumption that the limited series of Wynder and Segi are representative of the characteristics of Japanese in general and that our own equally limited series is similar to the population of the United States.

At any rate, as Table 5 shows, the Roswell Park series had an average of 30.2 years spent menstruating, as compared to around 21 for the Segi and Wynder series. On the other hand, Wynder's series experienced about six and Segi's about seven years of lactation, as compared to 1.2 for the Roswell Park series. Again, the Japanese series spent a longer amount of their lifetimes in pregnancy, and, at a given age, a longer number of years postmenopause than the U. S. group. We applied our dynamic risk differentials (from Figures 1 and 3) to these numbers to see whether the relative risks calculated from them were reminiscent of the relative risk based on incidence reported in Japan and the United States. The last column in the table shows the observed relative risk based on national statistics in the two countries to be 5.5. The next to last column shows the relative risks in the United States as compared to Japan,

Table 5—Relative Risks of Breast Cancer—Japan and United States, Estimated by Applying Dynamic Risk Differentials to Lactation and Menstrual Experience

Country	Number of Menstrual Years	Number of Lactation Years	Number of Pregnancy Years	Number of Post-Meno. Years	Calculated Relative Risk U.S./Japan	Observed Relative Risk U.S./Japan
U. S. (RPMI) Age at admission: 55–64	30.2	1.2	1.8	3.8		
Japan (Segi)[10]	19.9	7.0[12]	3.3	6.8	7.9	5.5[11]
Japan (Wynder)[13]	23.5	5.8	2.4	5.3	3.7	5.5[11]
Japan (average of Segi and Wynder data)	21.7	6.4	2.9	6.0	5.3	5.5[11]

calculated through applying the dynamic risk differentials to the years spent in various activities as reported by Wynder and Segi. It is interesting that the calculated relative risks of 7.9 and 3.7 are not greatly different from that actually observed. For the combined results of Segi and Wynder, shown in the last row, the calculated relative risk is 5.3 as compared to the actual 5.5. Despite the closeness of the predicted to the actual risks, our previous cautions regarding the bases of the predictions must be recalled.

To summarize, in pursuing our program in the epidemiology of mammary cancer, we have obtained evidence that menstrual activity and lactation are related to the disease. This relationship was apparent in a static analysis comparing experience of cases and controls at a point in time through conventional direct standardization and through matching technics. The dynamic risk analysis, when applied to differences in periods of time spent in menstrual and nursing activity, again suggested the importance of these variables. The size of the risk differentials derived seem small. But it would appear that, applied over the entire span of life, these differentials might account for a significant portion of the relative breast cancer incidence indicated in our comparison of Japan and the United States.

Results so far indicate strong support for the relation of menstrual history to risk of breast cancer. With respect to lactation history, the data suggest a more complex situation. With short histories of lactation (up to 17 months) the risk of breast cancer appears to increase, while thereafter, the risk of breast cancer declines until, at about 36 months and more, the net effect is a reduction of risk to levels consonant with those seen in comparisons of Japan with the United States. Our study of breast cancer cases and random controls throughout Buffalo and Kenmore, New York, will hopefully produce further evidence on this and other aspects of the relation of menstrual and lactation history to breast cancer.

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This paper was presented before the Epidemiology Section of the American Public Health Association at the Ninetieth Annual Meeting in Miami Beach, Fla., October 15, 1962.