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Age at First Birth and Breast Cancer Risk *

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An international collaborative study of breast cancer and reproductive experience has been carried out in 7 areas of the world. In all areas studied, a striking relation between age at first birth and breast cancer risk was observed. It is estimated that women having their first child when aged under 18 years have only about one-third the breast cancer risk of those whose first birth is delayed until the age of 35 years or more. Births after the first, even if they occur at an early age, have no, or very little, protective effect. The reduced risk of breast cancer in women having their first child at an early age explains the previously observed inverse relationship between total parity and breast cancer risk, since women having their first birth early tend to become ultimately of high parity. The association with age at first birth requires different kinds of etiological hypotheses from those that have been invoked in the past to explain the association between breast cancer risk and reproductive experience.

One of the most consistently observed epidemiological characteristics of breast cancer is the inverse association between the number of children a woman has borne and her risk of developing the disease. This association has been observed in all geographic areas and ethnic groups in which it has been studied. The association has been interpreted as indicating that some concomitant of pregnancy protects against the later development of breast cancer, the amount of protection being related to the number of pregnancies.

Analyses of data from a recent international collaborative study have shown that breast cancer risk is strongly correlated with age at first pregnancy (Lowe & MacMahon, 1970; Salber, Trichopoulos & MacMahon, 1969; Valaoras et al., 1969; Yuasa & MacMahon, 1970; and Lin, Chen & MacMahon; Ravnihar, MacMahon & Lindtner; Mirra & Cole, unpublished data). These analyses were based on the women's ages at their first pregnancy, even if that pregnancy aborted. Differences between cases and controls with respect to frequency of abortion were observed in only a few centres and were in the direction which suggested increased risk associated with abortion—contrary to the reduction in risk associated with full-term births. Therefore, it seemed worth while to conduct analyses restricting attention to the age at which the first full-term birth occurred. The details are presented in this paper. The analysis has also been extended to take a more detailed account of possible interrelationships with other variables and to examine the effect of age at confinements, other than the first.

METHODS

The case-control study which is the source of these data has been described previously (MacMahon et

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TABLE 1
NUMBER OF BREAST CANCER CASES AND CONTROLS INTERVIEWED IN THE VARIOUS STUDY CENTRES

Centre	Numbers included in present analyses						Numbers excluded [a]	
	Cases			Controls				
	Non-parous	Parous	Total	Non-parous	Parous	Total	Case	Control
Boston, USA	203	374	577	467	1 262	1 729	29	78
Glamorgan, Wales	161	446	607	321	1 492	1 813	12	37
Athens, Greece	216	579	795	554	1 910	2 464	4	6
Slovenia, Yugoslavia	153	601	754	419	1 862	2 281	18	27
São Paulo, Brazil	112	420	532	229	1 298	1 527	5	28
Taipei, Taiwan	34	177	211	55	589	644	3	4
Tokyo, Japan	224	623	847	409	1 832	2 241	2	9
All centres	1 103	3 220	4 323	2 454	10 245	12 699	73	189

[a] Women whose interview was rated " unreliable " by the interviewer and those for whom parity or age at first birth was not recorded are excluded.

al., 1970). It was conducted in seven areas of the world; the populations included exhibited a wide range of incidence rates for breast cancer—from a high of 55 per 100 000 persons per year in Boston, USA, to about 10 per 100 000 persons in Tokyo, Japan, and Taipei, Taiwan. As far as possible, the cases included all female residents of the study areas who were hospitalized for a first diagnosis of breast cancer during the study period. The controls were patients hospitalized in the same hospitals for conditions other than breast cancer. The 3 eligible patients in the beds closest to that of the index case were interviewed for each breast cancer patient interviewed. Eligibility required being a resident of the study population, never having had cancer of the breast and being over 35 years of age (unless the breast cancer patient was under 35 years of age, in which event an age-match within 2 years of the breast cancer patient's age was required). The interview form and the study protocol were the same for all centres. Coding, data-processing and analyses for all study areas were carried out in a single co-ordinating centre.

In all, more than 4000 breast cancer cases and nearly 13 000 control patients were interviewed. In 5 of the centres, the breast cancer cases included 80% or more of the cases known to have occurred during the study period. In 2 centres total ascertainment was not possible but the interviewed cases are believed to have represented about 50% of all incident cases in one (Tokyo) and about 70% in the other (São Paulo, Brazil).

For the purpose of the present analyses, her age at the time of birth of each of her full-term children was computed for each woman from her own and her children's dates of birth. Abortions—defined as pregnancies with foetal death prior to the fifth month—were excluded, but children stillborn at 5 or more months' gestation were included. " Parity " is also defined in terms of births at or after the fifth month of pregnancy, whether liveborn or stillborn. Single and ever-married women are included. In 5 of the 7 centres (all but Slovenia and São Paulo) single women were not questioned about their reproductive histories and have been assumed to be nulliparous. A few interviews (56 cases, 128 controls) were rated as " unreliable " by interviewers; these have been excluded. Also excluded are 11 cases and 31 controls for whom age at first birth is unknown. The numbers of women on whom the present analyses are based are given in Table 1.

FINDINGS

Age at first birth

Table 2 shows the relationship between total parity and breast cancer risk. In this table, the risk for

TABLE 2
ESTIMATES OF RELATIVE RISK[a] OF BREAST CANCER, BY PARITY

Centre	Parity					
	0	1	2	3	4	≥5
Boston	100	76	81	64	59	54
Glamorgan	100	68	60	63	61	42
Athens	100	76	93	77	68	58
Slovenia	100	93	89	84	83	90
São Paulo	100	78	87	60	62	57
Taipei	100	74	48	41	47	48
Tokyo	100	82	84	60	59	34

[a] Risk relative to an arbitrary risk of 100 for the non-parous (see text).

women of any specified parity relative to that of non-parous women is calculated from the usual formula ad/bc, where a is the number of cases of that parity, b the number of controls in the same parity, and c and d the number of non-parous cases and controls, respectively. The trends are not regular but, except in Slovenia where the trend is weak and in Tokyo where it is strong, estimated risks for women of parity 5 or more are between 40% and 60% of those of the nulliparous. This is the usual relationship between parity and breast cancer risk, as observed many times by previous workers.

Table 3 shows the association of breast cancer risk with age at first birth. In all 7 centres, risk increases with increase in the age at which a woman bore her first child. In 5 of the centres the trend is strong and regular, with women who had their first birth when under 20 years of age having only about one-third the risk of those whose first birth occurred at the age of 35 years or older. In Slovenia, the trend appears not to be as strong as in the other centres. In this centre, for women with first births after the age of 20 years the trend is consistent with that in other centres, but the relative risk for women with births under the age of 20 years is inconsistently high. In Taipei, the trend is irregular, perhaps as a consequence of the small numbers in this centre, but the impression of low breast cancer risk for women having their first birth at an early age is present. It is interesting that the trend is reasonably consistent between centres in spite of the considerable differences in the distribution of women by age at first birth. For example, nearly 30% of the women in São Paulo, but only 7% of those in Glamorgan, Wales, had a birth before the age of 20 years, but the relative risks for women in this group are similar in the two centres. It is also of interest that the reduction in relative risk appears not to be dependent on the over-all level of breast cancer rates in a particular area.

The risks for women who had their first birth between the ages of 30 and 34 years approach those of non-parous women, and, in all centres, women whose first birth was delayed until the age of 35 years or over actually had higher risks than nulliparous women.

In view of the general similarity of these trends, it seemed reasonable to pool the data for all centres. Table 3 gives an estimate, from the pooled data, that the breast cancer risk for women having their first birth under the age of 20 years is about half that for nulliparous women and 40% of that for women whose first birth is delayed until the age of 35 years or over.

To evaluate the effect of the assumption made in 5 centres, that single women were non-parous, the bottom row of Table 3 shows the pooled relative risks based on married women only. The values are almost identical with those based on all women, and the remaining analyses are therefore based on all women regardless of marital status.

Pooling of the data from all centres enables estimates of relative risk for individual years of age at first birth to be made. These values, for ages of 14 years to 41 years, inclusive, are plotted in the accompanying figure. The figure suggests that, at least up to about 30 years of age, breast cancer risk increases linearly with increasing age at first birth. For women having first births when under 20 years of age, the risk continues to decrease as age at first birth decreases; women with first births when under 18 years of age have only about one-third of the breast cancer risk of those with first births when over 35 years. The number of women having first births in the individual ages after 30 years is small, even when the data for all centres are combined, and the estimates of relative risk have fairly large variances. It is not clear, therefore, whether the linear trend continues for first births after the age of 30 years.

Relationship to total parity

We must of course examine the possibility that the association of breast cancer risk with age at first

TABLE 3
PERCENTAGE DISTRIBUTION OF CASES AND CONTROLS, AND ESTIMATES OF RELATIVE RISK OF BREAST CANCER, BY AGE AT FIRST BIRTH

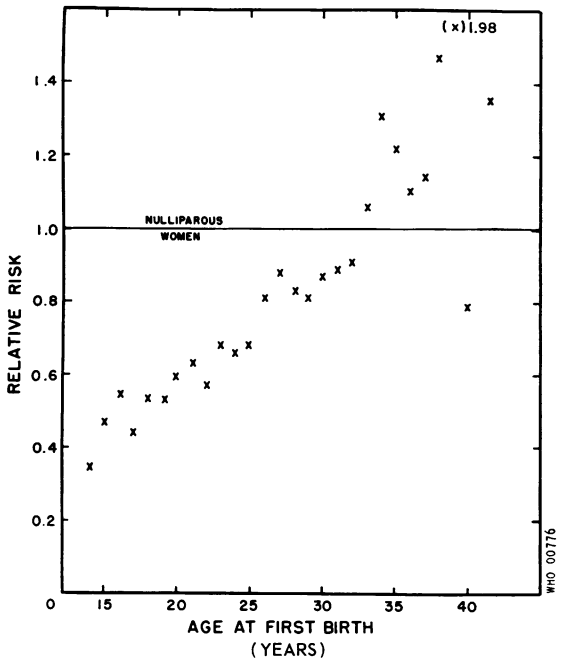
Group	Centre	Nulli-parous	Parous, age at first birth being:					Total
			<20	20–24	25–29	30–34	⩾35	
Cases	Boston	35.2	3.1	19.6	23.4	12.5	6.2	100.0
	Glamorgan	26.5	3.8	27.2	24.5	11.7	6.3	100.0
	Athens	27.2	8.2	22.5	22.5	14.0	5.7	100.1
	Slovenia	20.3	5.0	27.4	28.4	12.6	6.2	99.9
	São Paulo	21.5	20.5	39.1	13.2	3.4	2.3	100.0
	Taipei	16.1	16.6	41.7	14.7	8.1	2.8	100.0
	Tokyo	26.5	2.8	29.4	27.9	9.1	4.4	100.1
	All centres	25.5	7.4	27.9	23.4	10.7	5.1	100.0
Controls	Boston	27.0	7.5	27.2	23.5	10.7	4.1	100.0
	Glamorgan	17.7	6.7	37.0	24.6	10.6	3.4	100.0
	Athens	22.5	13.2	26.1	23.6	10.9	3.7	100.0
	Slovenia	18.4	5.7	33.7	27.3	10.2	4.8	100.1
	São Paulo	15.0	29.3	42.1	9.8	2.9	0.9	100.0
	Taipei	8.5	16.2	48.5	20.7	4.8	1.4	100.1
	Tokyo	18.2	7.5	41.4	24.5	6.2	2.2	100.0
	All centres	19.3	11.2	34.9	22.7	8.6	3.2	99.9
Relative risk [a]	Boston	100	32	55	76	90	117	—
	Glamorgan	100	38	49	67	73	124	—
	Athens	100	51	71	79	106	127	—
	Slovenia	100	81	74	94	112	118	—
	São Paulo	100	49	65	94	84	175	—
	Taipei	100	54	45	37	89	106	—
	Tokyo	100	26	49	78	100	138	—
	All centres	100	50	60	78	94	122	—
Married only [b]	All centres	100	48	59	76	91	119	—

[a] Estimated risk relative to a risk of 100 for the non-parous.
[b] Relative risk based on married women only.

birth reflects merely the low parity of the breast cancer patients—women of low parity tending to begin their reproductive lives late. The fact that, in all centres except Taipei, the relative risks associated with first birth under the age of 20 years (Table 3) are lower than those for women of parity 5 or more (Table 2) suggests that age at first birth is the more relevant variable. However, the question can be approached more directly.

Table 4 shows the observed numbers of cases with first births under the age of 20 years, together with expected values based on the control series adjusted

RELATIVE RISK[a] OF BREAST CANCER ACCORDING TO AGE AT FIRST BIRTH; DATA FOR ALL CENTRES COMBINED



[a] Relative to a risk of 1.0 for nulliparous women.

for pertinent variables, including parity. The use of parity-specific rates in the control series does shift the expected values towards the observed values in all centres. However, the shifts are small and, except in Slovenia and Taipei where the differences were small even before correction for parity, substantial differences remain after this adjustment.

That the association of breast cancer risk with age at first birth is not merely a reflection of the low parity of breast cancer patients can also be demonstrated by restricting attention to women who have borne only one child. Relative risks for such women, according to age at which their only birth occurred, are shown in Table 5. Except in Slovenia and Taipei, which again show irregular patterns, there is in each centre a sharp increase in risk as age at confinement increases.

Births after the first

Since the increased risk associated with delayed first birth is not explained by the low parity of breast cancer patients, we must consider the possibility that the late first births of such women explain the previously noted association of risk with low parity. Table 6 shows observed and expected numbers of cases having births after the first. In this table expected values are based on the distribution of the controls specific for each individual year of age at first birth. If births after the first were associated with

TABLE 4

OBSERVED NUMBER OF BREAST CANCER CASES WITH FIRST BIRTHS WHEN UNDER 20 YEARS OF AGE AND EXPECTED VALUES COMPUTED FROM THE CONTROL SERIES

Centre	Observed	Expected,[a] with adjustment for:			
		No. variables	Parity	Age at interview	Duration of schooling
Boston	18	38.2	34.7	37.7	37.5
Glamorgan	22	36.5	33.5	35.9	35.4
Athens	65	98.2	94.0	99.7	93.2
Slovenia	38	41.6	41.4	41.8	41.6
São Paulo	117	144.6	135.8	144.2	140.5
Taipei	35	31.3	32.6	33.6	28.1
Tokyo	24	57.1	47.8	52.5	52.5

[a] The expected values are based on the distribution of the control series, specific for the stated variables.

TABLE 5

ESTIMATES OF RELATIVE RISK OF BREAST CANCER BY AGE AT DELIVERY, FOR WOMEN OF PARITY 1 ONLY

Centre	Relative risks,[a] age at delivery being:						No. of:	
	<20	20–24	25–29	30–34	⩾35	Any age	Cases	Controls
Boston	19	72	60	107	118	76	77	233
Glamorgan	(50) [b]	29	100	55	106	68	117	345
Athens	44	64	65	120	81	76	129	433
Slovenia	123	81	83	126	88	93	136	399
São Paulo	66	70	102	(74) [b]	(175) [b]	78	63	165
Taipei	(92) [b]	(61) [b]	(121) [b]	(50) [b]	(81) [b]	74	22	48
Tokyo	52	61	67	119	152	82	135	302
All centres	58	62	77	98	104	78	679	1 925

[a] Relative risks are expressed relative to a risk of 100 for non-parous women. Estimates are based on direct comparison of cases and controls, without adjustment.

[b] Values for cells containing less than 20 controls are shown in parentheses.

TABLE 6

OBSERVED AND EXPECTED NUMBERS OF BREAST CANCER CASES HAVING SPECIFIED NUMBERS OF BIRTHS AFTER THE FIRST, ADJUSTED FOR AGE AT THE FIRST BIRTH

Centre	No. of cases having 1 or more births	No. of births after the first											
		None		1		2		3		4–8		⩾9	
		Obs.	Exp.[a]	Obs.	Exp.[a]	Obs.	Exp.[a]	Obs.	Exp.[a]	Obs.	Exp.[a]	Obs.	Exp.[a]
Boston	374	77	78.6	122	109.2	75	77.4	42	46.2	58	59.4	0	3.3
Glamorgan	446	117	122.5	138	137.6	91	85.4	51	42.7	45	53.8	4	4.1
Athens	579	129	148.4	210	178.1	109	105.5	64	69.1	62	74.2	5	3.7
Slovenia	601	136	137.8	163	161.5	110	114.6	75	77.8	106	100.9	11	8.4
São Paulo	420	63	58.4	100	79.7	59	68.9	47	50.8	118	122.9	33	39.4
Taipei	177	22	19.4	26	24.7	29	34.0	29	29.3	62	62.6	9	7.1
Tokyo	623	135	128.6	186	150.4	120	121.6	95	94.2	86	123.3	1	5.0
All centres	3 220	679	693.7	945	841.2	593	607.4	403	410.1	537	597.1	63	71.0
Relative risk [b]	—	100		116		101		102		93		92	

[a] Expected values are based on rates in the control series specific for individual years of age at first birth.

[b] Relative to a risk of 100 for women having no births after the first; data for all centres combined.

decreased breast cancer risk, the number of cases who had no births after the first would be higher than the expected value; it is actually slightly lower. There is a deficit of cases with 4 or more births after the first (observed 600, expected 668.1), but the risk for this category is reduced only to 93 relative to 100 for women having no subsequent births. Moreover, the deficit of cases with 4 or more subsequent births is substantial only in Tokyo. It seems, therefore, that births after the first have relatively little influence on breast cancer risk, and the relationship between breast cancer risk and parity results primarily from the fact that age at first birth and ultimate total parity are highly correlated.

We must still enquire whether births after the first may exert a protective influence if they occur at a young age. Table 7 shows observed and expected distributions of women who had at least one birth when under the age of 25 years according to the number of births they had under that age. The expected values are computed, taking account of the specific year of age at the first birth. Using the pooled data from all centres, there is a suggestion that the risk for women having more than one birth when under the age of 25 years is somewhat lower than for those having only one. However, the reduction is relatively small. Thus, among women who had a second birth when under the age of 25 years, the mean age at the second birth (all centres combined) was 22.1 years. The figure indicates that a first birth at this age would be associated with a reduction in risk of about 40%. The data in Table 7 indicate that the additional reduction of risk associated with more than one birth when under the age of 25 years is about 13%.

In all centres combined, there were 319 cases in which a first birth occurred under the age of 20 years. Of these, 78 had more than one birth when under this age. The expected number having more than one birth when under the age of 20 years (68.5), computed with adjustment for age at which the first birth occurred, is actually lower than the observed. If births other than the first at an early age conferred additional protection, the expected value would of course be higher than the observed. In summary, it seems that if births after the first have any additional protective influence it is substantially less than that of a first birth at the same age.

Table 3 indicates that women with first births when over 35 years of age have higher risks than nonparous women. In Table 8, therefore, relative risks associated with births other than the first occurring over the age of 35 years are examined. The data are shown separately for women whose first birth

TABLE 7

OBSERVED AND EXPECTED NUMBERS OF BREAST CANCER CASES WITH SPECIFIED NUMBERS OF BIRTHS PRIOR TO THE AGE OF 25 YEARS

Centre	No. of cases	No. of births prior to 25 years					
		1		2		⩾3	
		Obs.	Exp.[a]	Obs.	Exp.[a]	Obs.	Exp.[a]
Boston	131	89	76.0	31	38.3	11	16.7
Glamorgan	187	122	113.3	46	51.6	19	22.1
Athens	243	137	125.3	67	76.6	39	41.1
Slovenia	245	158	143.9	64	68.7	23	32.4
São Paulo	321	109	97.9	117	115.7	95	107.4
Taipei	123	46	52.1	47	39.3	30	31.6
Tokyo	272	172	173.9	80	76.7	20	21.5
All centres	1 522	833	782.4	452	466.9	237	272.8
Relative risk[b]	—	68		61		55	

[a] The table is based on women with at least 1 birth before the age of 25 years. Expected values are based on rates in the control series specific for individual years of age at first birth.

[b] Relative to a risk of 100 for women with no births before the age of 25 years.

TABLE 8

OBSERVED AND EXPECTED NUMBERS OF BREAST CANCER CASES HAVING BIRTHS OTHER THAN THE FIRST AT THE AGE OF 35 YEARS OR OLDER

Centre	Women whose first birth occurred at 35 years of age or older			Women whose first birth occurred under 35 years of age		
	No. of women	No. having 1 or more other births		No. of women	No. having 1 or more births at 35 years of age or older	
		Obs.	Exp.[a]		Obs.	Exp.[a]
Boston	36	18	17.9	338	118	124.6
Glamorgan	38	12	8.6	408	131	125.3
Athens	45	25	11.7	534	127	116.0
Slovenia	47	28	21.9	554	221	183.7
São Paulo	12	6	4.9	408	94	93.6
Taipei	6	4	3.3	171	54	50.5
Tokyo	37	12	12.5	586	141	175.8
All centres	221	105	80.8	2 999	886	869.5
Relative risk[b]	—	157		—	103	

[a] Expected values are based on rates in the control series specific for individual years of age at first birth.

[b] Relative to a risk of 100 for women in the same age-at-first-birth category who had no subsequent births when aged 35 years or more.

occurred at 35 years of age or over and for women whose first birth occurred before the age of 35 years. In each case, expected values are based on the control series with adjustment for age at first birth. In women whose first birth was delayed until the age of 35 years, additional births do seem to be associated with an increase in risk. However, no such increase in risk is seen for women having births when over the age of 35 years if their first birth occurred prior to that age.

Socio-economic status

Socio-economic status, being related to both age at first birth and breast cancer risk, must also be examined as a possible confounding variable. In our data, the duration of a patient's schooling was found to be the measure of socio-economic status most closely related to breast cancer risk. As shown in Table 4, adjustment for this variable does reduce the expected values for patients with births under the age of 20 years but, again, the reductions are relatively small and substantial differences between expected and observed values persist after the adjustment.

We have also examined the possibility that the association of breast cancer risk with age at first birth may explain the previously observed association of the disease with socio-economic status. However, in those centres where differences exist between cases and controls with respect to socio-economic status —in particular Athens, São Paulo and Tokyo— the extent of the differences is not substantially changed by adjusting for age at first birth.

Age at diagnosis of cancer

In at least some of the areas included in this study, changes have occurred over time in the usual age at first confinement in the female population. We must therefore consider the possible effect of age differences between cases and controls at the time of interview—in effect, the age at diagnosis of breast cancer. The computation of expected values using age-specific rates (Table 4) leaves the expected values virtually unchanged, and age at interview can be ignored as a variable likely to confound the association of breast cancer risk with age at first birth.

It is also of interest to know whether the association of breast cancer risk with age at first birth differs between cases diagnosed at different ages. Table 9 shows the risks for women with first births when under the age of 25 years relative to those for women with first births when aged 30 years or over, according to age at diagnosis of cancer. Two estimates are given of the values for the pooled data. One of these, A, is based on the simple sums of the numbers of cases and controls in the specific age-group in all centres. This estimate has the disadvantage that the different centres contribute in different proportions to the several age-at-diagnosis groups and also exhibit different strengths of the association between breast cancer risk and age at first birth. For example, the association with age at first birth appears to be particularly strong in Tokyo (Table 3) and the age distribution of the cases in Tokyo is lower than that in the other centres. A second estimate for the pooled data, B, is therefore derived by obtaining a weighted mean of the values shown for individual centres, the weights being the numbers of controls in the various centres. The weights are the same in all age-at-diagnosis groups.

Within individual centres, trends in Table 9 are irregular—presumably because of the small numbers in many of the cells. Both sets of estimates from the pooled data suggest less reduction in the relative

TABLE 9

ESTIMATES [a] OF RISK OF BREAST CANCER FOR WOMEN WITH FIRST BIRTHS BEFORE THE AGE OF 25 YEARS, RELATIVE TO RISKS FOR WOMEN WITH FIRST BIRTHS AT 30 YEARS OR OLDER, BY AGE AT DIAGNOSIS OF CANCER

Centre	Age at diagnosis				
	<45	45–54	55–64	65–74	⩾75
Boston	56	28	68	81	62
Glamorgan	54	61	51	63	72
Athens	63	54	37	92	77
Slovenia	65	66	75	57	113
São Paulo	42	64	82	—	—
Taipei	70	29	—	—	—
Tokyo	38	60	33	37	—
All centres;					
A [b]	54	55	59	62	70
B [c]	55	55	56	66	81

[a] Estimates are not shown for cells containing less than 5 expected cases.

[b] Estimates derived from actual sums of the data in each age-group from all centres.

[c] Weighted means of the values shown for individual centres. Weights are the numbers of controls included, as shown in Table 1.

risk among cases first diagnosed after 65 years of age than in younger age-groups. However, this difference is relatively small and a protective effect of a first pregnancy under the age of 25 years is seen in all age-categories.

Age at marriage

Since the risk of breast cancer in married, nulliparous women is similar to that in single women (MacMahon et al., 1970) there seems no reason to suspect that the association observed with age at first birth is an indirect expression of an association between breast cancer risk and age at marriage. However, this question can be explored directly by examining the age at marriage of nulliparous women. Such an examination is shown in Table 10.

Again, numbers are too small for examination of trends in individual centres. The pooled data for all centres do suggest lower risks for nulliparous women married under the age of 25 years than for those married later. However, relative to the trend in risks associated with age at first birth (Table 3), that with age at marriage is weak. In addition, the deficit of cases observed among nulliparous women first married under the age of 20 years is confined to 2 centres. If these are excluded (bottom line of Table 10) the trend disappears. We have no explanation for the appearance of this feature in these two centres. In view of the relatively small change in risk associated with it and its limitation to 2 of the 7 centres, we conclude that early marriage is not associated with reduction in risk of cancer of the breast, unless it is associated with early confinement.

DISCUSSION

This is by no means the first study in which a difference between breast cancer cases and controls in age at first birth has been observed. In many previous comparisons of breast cancer cases and unaffected women the cases have been found to be, on average, older at marriage, at first pregnancy, or at both (Lane-Claypon, 1926; Wainwright, 1931; Gilliam, 1951; Stocks, 1955; Segi et al., 1957; Wynder, Bross & Hirayama, 1960; Levin et al., 1964). However, previous workers seem not to have considered the differences to be sufficiently important to warrant detailed exploration. An apparent lack of interest in the relationship may have resulted from failure to realize the magnitude of the differences in relative risk that underlie it. This lack of recognition of the strength of the relationship can be attributed primarily to analyses utilizing summary statistics such as means and ridits. In countries where most epidemiological studies of this disease have been undertaken, the proportion of women who have their first birth at an early age is relatively small, and summary statistics fail to reveal the high risks experienced by small segments of the population. For example, in the present data from Boston, the mean age at first birth was 27.1 years in the cases and 25.5 years in the controls. While this difference is statistically highly significant it would hardly lead one to suspect the almost four-fold range of relative risks shown in Table 3.

Most previous workers have given more attention to the relationship of breast cancer with total parity than to that with age at first birth. Stocks (1957), among past workers, appears to have come closest to elucidating the nature of the relationship between reproductive experience and breast cancer risk. In a series of 421 breast cancer cases and 718 age-matched controls he noted a deficit of cases first married before the age of 25 years. He also noted that, when differences in age at marriage were

TABLE 10

OBSERVED AND EXPECTED NUMBERS OF BREAST CANCER CASES, BY MARITAL STATUS AND AGE AT FIRST MARRIAGE; NON-PAROUS CASES ONLY

Centre	Observed or expected	Never married	Ever-married, age at first marriage being:					Total
			<20	20–24	25–29	30–34	⩾35	
Boston	Obs.	114	8	16	25	8	28	199
	Exp.[a]	108.0	7.3	21.7	19.4	12.1	30.5	199.0
Glamorgan	Obs.	61	3	25	32	12	27	160[b]
	Exp.[a]	61.2	3.8	28.5	28.4	12.3	25.9	160.1
Athens	Obs.	80	16	27	29	25	34	211
	Exp.[a]	74.5	27.5	32.1	31.3	20.4	25.2	211.0
Slovenia	Obs.	92	1	13	17	16	17	156
	Exp.[a]	89.9	1.9	11.7	17.9	12.0	22.6	156.0
São Paulo	Obs.	67	18	17	3	3	8	116
	Exp.[a]	55.2	26.0	20.1	7.8	3.1	3.9	116.1
Taipei	Obs.	1	10	14	4	2	2	33
	Exp.[a]	8.2	8.6	11.8	0.9	0.6	2.9	33.0
Tokyo	Obs.	65	20	66	40	17	15	223
	Exp.[a]	58.3	18.6	75.7	46.4	13.6	10.5	223.1
All centres	Obs.	480	76	178	150	83	131	1 098
	Exp.[a]	455.3	93.7	201.6	152.1	74.1	121.5	1 098.3
Relative risk,[c] all centres		105	81	88	99	112	108	—
Relative risk,[c] all centres except Athens and São Paulo		102	104	90	104	109	96	—

[a] Expected values are derived from the control gro up of the same centre, adjusted for age at interview (5-year groups).

[b] Excludes 1 case with unknown age at marriage.

[c] Relative to a risk of 100 in all non-parous wom en.

allowed for, breast cancer cases first married under the age of 25 years had a relative deficit of confinements whereas those first married over the age of 25 years did not. Stocks did not consider age at first birth directly and so did not note that the deficit of confinements among cases married when under 25 years occurred solely with respect to the first confinement. The strength of the relationship was not as clear as it would have been if the group first married under the age of 20 years had been separated from those first married between the ages of 20 and 25 years. Nevertheless, Stocks (*op. cit.*) was able to conclude that a dearth of confinements during the first 10 years or so of reproductive life increases the risk of breast cancer but that, if marriage is delayed, the number of confinements is unimportant. Kaplan & Acheson (1966) confirmed the first part of this conclusion, noting a deficit of births within 10 years of menarche among breast cancer cases which was statistically highly significant even though based on only 86 cases and 87 controls.

Our findings suggest that:

(1) The protective effect of early reproductive experience is related to age at confinement, rather than to age at marriage.

(2) The effect is a function particularly of age at first confinement, although it is possible that subsequent deliveries, if they also occur at an early age, may have some additional protective effect.

(3) The relationship is much stronger than previously suspected, women first confined under 18 years of age having only 40% of the breast cancer rates of nulliparous women, and even lower relative risks in some areas.

(4) Age at first confinement is a much more important factor than the total number of births; indeed, the latter probably has no association with breast cancer risk except through its association with age at first birth.

Several aspects of these findings make it necessary to revise existing hypotheses about the protective mechanisms of pregnancy. The striking reduction of risk associated with a single pregnancy of only 9 months' duration implies that the reduction is not explained by decreased exposure to causative agents during the pregnancy alone. The pregnancy must be associated with changes that bring about reduction either in exposure or in response to exposure over a prolonged period of time.

That it is the *first* confinement with which reduction in risk is associated suggests that the first pregnancy induces irreversible changes that either render the breast tissue itself less susceptible to induction of cancer or reduce the carcinogenic stimulus to the breast. The fact that early first pregnancy is associated with reduction in breast cancer risk even among women aged 75 years and older indicates the long duration of the changes that must be induced.

The effect of the first pregnancy being more marked the earlier it occurs might be explained by one or more of several mechanisms. First, a pregnancy at a young age, because of special characteristics of such pregnancies, may be particularly protective. Second, exposure to carcinogens may be particularly high in younger women—pregnancy in the young would then exert its protective effect during a period which would otherwise be associated with high risk of tumour induction. Third, the first pregnancy may act as, or possibly is itself made possible by, a threshold type of biological phenomenon which brings to an end a period of high risk of tumour induction; the earlier the pregnancy, the shorter would then be the period of risk and the lower the probability of induction.

It has recently been suggested—in part on the basis of the known protective effect of early pregnancy—that the specific oestrogen fractions produced by a woman in the decade or so after puberty are important determinants of her life-time breast cancer risk (Cole & MacMahon, 1969; MacMahon & Cole, 1969). The data presented here would be compatible with this hypothesis if an early first pregnancy is associated with a favourable alteration in the oestrogen profile, or if the first pregnancy induced changes in the breast tissue rendering it less susceptible to oestrogen carcinogenesis. Data that would allow evaluation of either of these possibilities are lacking. Whether or not this specific hypothesis is correct, it is clear that there must be some potential carcinogenic experience to which post-pubertal girls are exposed and which can be markedly influenced by pregnancy.

In addition to indicating a protective influence of early pregnancy, our data suggest that late first pregnancies may actually increase risk. Women who had their first delivery after the age of 35 years had risks approximately 20% higher than those who were nulliparous. If a woman had had a first birth at an earlier age, later births after the age of 35 years did not appear to be associated with increased risk. However, if the first birth was delayed until the age of 35 years subsequent births appeared to be associated with an additional increase in risk (Table 8). This phenomenon most likely has a mechanism quite different from that underlying the protective effect of early pregnancy. Of possible relevance are observations of the effect of pregnancy on chemically induced mammary tumours in the rat. A single pregnancy prior to the feeding of a carcinogen results in a decreased frequency of mammary tumours; further pregnancies do not greatly influence the number of tumours (Moon, 1969). The situation appears therefore to be quite analogous to the effect of early pregnancy in women. However, pregnancy occurring *after* chemical induction of breast tumours in rats is associated with acceleration of tumour growth and increase in the number of active centres per rat (Dao & Sunderland, 1959). If, in humans, breast cancer is induced at some point during the reproductive years, the later a woman has her first pregnancy the more likely it is that an antecedent neoplastic change has occurred. In view of the rapid proliferation of breast tissue during pregnancy, it is understandable that pregnancy could be associated with stimulation and proliferation of any cancerous cells present in the breast tissue at the time of the pregnancy. Thus, early first pregnancies may tend to occur prior to induction and confer protection, while late first pregnancies may be likely to occur after induction and produce a deleterious effect.

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RÉSUMÉ

ÂGE AU MOMENT DE LA NAISSANCE DU PREMIER ENFANT ET RISQUE DE CANCER DU SEIN

Une enquête collective à l'échelon international destinée à étudier les rapports entre le risque de cancer du sein et la durée de la lactation a mis en évidence une corrélation entre la gravité du risque et l'âge de la femme lors de la naissance du premier enfant. Cette association est analysée plus en détail dans le présent article où seules ont été retenues les grossesses menées à terme et où l'on a tenu compte des naissances autres que la première.

L'étude a porté sur 4323 femmes atteintes de cancer du sein et sur 12 699 malades témoins souffrant d'autres affections. Elle s'est déroulée dans sept régions offrant une gamme étendue d'incidences du cancer du sein (de 10 à 55 cas par 100 000 personnes); on a centralisé les réponses obtenues au cours d'un entretien standard aux fins de traitement et d'analyse.

On a constaté, dans tous les centres, une augmentation du risque de cancer du sein en fonction de l'âge de la femme lors du premier accouchement. L'ensemble des données indique que chez les femmes qui ont eu leur premier enfant avant l'âge de 18 ans, le risque est trois fois moins élevé que chez celles qui ont accouché pour la première fois à 35 ans ou plus tard. Lorsque la première naissance a eu lieu entre 30 et 34 ans, le risque est du même ordre que celui auquel sont exposées les nullipares; si elle s'est produite après 35 ans, le risque est plus élevé que chez les femmes qui n'ont pas eu d'enfants.

Même quand elles se succèdent chez des femmes très jeunes, les grossesses ultérieures n'ont qu'une très faible influence favorable sur la gravité du risque. Lorsque la première naissance a lieu après 35 ans, le risque est légèrement augmenté par de nouvelles grossesses. Chez la femme de plus de 35 ans qui a eu un enfant avant cet âge, de nouvelles maternités n'accroissent apparemment pas le risque.

La fréquence moindre du cancer du sein chez les femmes qui ont eu leur premier enfant très tôt explique le fait, déjà constaté, que le risque est réduit en cas de multiparité élevée, car ce sont généralement les femmes qui ont été mères précocement qui ont par la suite un grand nombre d'enfants.

Aucune des relations qui viennent d'être décrites n'est affectée sensiblement par d'éventuelles différences de niveau socio-économique ou d'autres paramètres entre malades atteintes de cancer du sein et malades témoins. L'effet protecteur d'une maternité précoce est manifeste, quel que soit le moment où le diagnostic de la maladie est posé, mais il semble moins prononcé lorsque l'affection est dépistée après l'âge de 75 ans.

Ces observations montrent la nécessité de réexaminer les hypothèses avancées pour expliquer le mécanisme de la protection contre le risque de cancer du sein conférée par la grossesse. Elles donnent à penser que, durant les premières années de la période de reproduction, des phénomènes d'une portée considérable influent sur le risque global auquel la femme est exposée au cours de son existence.

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