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REPRODUCTIVE HISTORY AND BREAST CANCER IN A POPULATION OF HIGH FERTILITY, COSTA RICA, 1984-85

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The relationship between breast cancer and women's reproductive history in Costa Rica was analyzed using logistic regression methods on data from 171 breast cancer cases and 826 population-based controls aged 25-58 years. The risk of breast cancer in nulliparous women under age 45 was 3 times that for parous women in the same age group. Women over 44 years of age with a parity greater than 4 had a risk of breast cancer of 0.3 compared to women of the same age but with a parity of 1-4. Neither breast-feeding nor birth interval showed an overall association with breast cancer independent of parity. Women with early age at first birth had a lower relative risk of breast cancer than women aged 20-24 at first birth, but only in two subgroups—women aged 45 and over and women with parity 1-4. Women without a completed pregnancy in the last 20 years had an elevated relative risk. However, results are not conclusive because some information is probably distorted by recall errors. Declines in fertility rates in the 1960s and 1970s may result in an increase of 30% in breast cancer incidence in Costa Rica between 1980 and the year 2000, according to the relative risks found in this study. In contrast, the effect of childlessness will probably not produce significant changes in national breast cancer trends.

The relationship between women's reproductive history and the risk of breast cancer has been the subject of many investigations (Kelsey, 1979). In most studies, investigators have found an increasing risk of breast cancer in women of low parity, especially in nulliparous women, and those with a late age at first birth. In some studies, investigators have also found a negative association between breast-feeding and breast cancer (Thomas, 1980). But because parity, age at first birth, and breast-feeding are usually correlated, it is unclear whether their effects on breast cancer are independent of each other. A multicenter World Health Organization study conducted in 7 areas in the 1960s concluded that age at first completed pregnancy is the only reproductive factor having an independent influence on breast cancer risk (MacMahon *et al.*, 1970). However, recent researchers have reached differing conclusions, restoring the importance of low parity and lack of breast-feeding as postulated independent risk factors for breast cancer (Thomas *et al.*, 1980; Byers *et al.*, 1985; Layde *et al.*, 1986; Helmrich *et al.*, 1983).

In 1984-85, we used a case-control design to study cervical and breast cancer in Costa Rica. The Costa Rican Demographic Association conducted the study in collaboration with the Centers for Disease Control, with additional assistance from the Costa Rican Ministry of Health, Costa Rican Social Security System, and Family Health International. Here we present our analysis of the association between breast cancer and the following aspects of women's reproductive history: parity, nulliparity, breast-feeding, age at first birth, recency of last birth, and birth interval. (The relationship of hormonal contraception to breast cancer and cervical cancer is the subject of separate reports: Lee *et al.*, 1987; Oberle *et al.*, 1986; Irwin *et al.*, in press.)

Our analysis examines whether these reproductive factors are independently associated with breast cancer and whether the relationships between these factors in a high-fertility population are similar to those found in developed countries.

BACKGROUND

Costa Rica is a small Central American country with 2.6 million inhabitants. Approximately half of the population is rural. Nearly two-thirds of the population inhabit the central highlands, usually called the Central Valley, where San José, the capital city, is located. Although a developing country in economic terms, Costa Rica's health status is advanced. In 1983, life expectancy was 74 years, and infant mortality was 18 per 1,000 (World Bank, 1984).

With the control of infectious diseases in Costa Rica, cancer has become the second leading cause of death (Bermudez, 1985). Among the female population, breast cancer is the third leading cause of cancer incidence and mortality (Sierra and Barrantes, 1986). Mortality rates for breast cancer have increased slightly over the past 20 years, to a 1983 rate of 13 per 100,000 women over 20 years of age. The incidence of breast cancer for Costa Rican women is less than half that of US white women of the same age (Rosero-Bixby and Grimaldo, 1987).

Between 1960 and 1975, the total fertility rate in Costa Rica declined sharply, from 7.3 to 3.7 children per woman. In 1983, this rate stood at 3.4 children (Rosero-Bixby, 1983). Nevertheless, for women older than 50, the age group with the highest incidence of breast cancer, the mean number of children per woman has not changed, because the fertility decline has occurred in younger cohorts.

The proportion of nulliparous women, which is about 8% by the time women reach menopause, has remained stable over 3 decades in Costa Rica (Casterline and Trussel, 1980). Fertility in women under 20 years of age has declined minimally over the past 3 decades, and the average age at marriage and average age at first birth have increased only slightly over this time period. Neither abortion nor breast-feeding have been important in the decline of Costa Rican fertility (Rosero-Bixby, 1981).

METHODS

Cases selected from the National Tumor Registry comprised all women between 25 and 58 years of age with breast cancer diagnosed between January 1, 1982, and March 31, 1984. If the Tumor Registry had inadequate information on address or histological type, we reviewed additional hospital records to

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obtain the necessary information. A total of 259 women were eligible as cases, and 174, or 67%, of them could be interviewed (Table I). Death of the patient (19%) was the main reason for not interviewing an eligible case.

Controls were selected using a multistage, stratified, probability household survey throughout Costa Rica. The sampling frame was based on maps and preliminary results from the June 1984 census. In each household sampled, women aged 25–59 years at the time of interview were eligible as controls. Older women were oversampled so that the age distribution of the controls would be frequency-matched to the age distribution of the combined group of all breast and cervical cancer cases in the study. During the survey, 938 women were selected as potential controls and 870 of them (93%) were interviewed (Table I).

Cases and controls were interviewed in their homes with a standard questionnaire modified from the questionnaire developed for the Cancer and Steroid Hormone Study (Centers for Disease Control, 1983). Interviews were conducted between September 1984 and February 1985 by female interviewers who had undergone an intensive week-long training course. The interviewers obtained extensive information about a woman's reproductive, medical, and sexual history. A life history calendar assisted in the recall of reproductive history and contraceptive use. Interviews lasted about 42 minutes.

Because interviews were conducted up to 3 years after the date of case diagnosis, we adjusted many variables to an index date. For each case, the index date was the patient's date of diagnosis. For controls, we assigned an index date of February 15, 1983, the midpoint of the period of case eligibility. Information recorded on the questionnaire and calendar allowed us to adjust variables to the index date. We excluded from the analysis women who were not 25–58 years old at index date. The analysis included 171 cases and 826 controls who were 25–58 years old at index date. Pregnancies and periods of contraceptive use which occurred after the index date were also excluded from analysis.

An index of economic status ranging from 1 to 17 was created, based on reported possession of 8 major household appliances. We considered a history of benign breast disease to be positive if a respondent reported a biopsy of a cyst or lump not resulting in a mastectomy. A woman had a family history of breast cancer if she reported that her mother, sisters, or daughters had had breast cancer. We considered a woman to have had a natural menopause if she was at least 35 years old, had not had a hysterectomy, and her last menstrual period had occurred more than 12 months before the interview period.

TABLE I - INTERVIEW OUTCOME FOR BREAST CANCER CASES AND CONTROLS

Interview outcome	Cases		Controls	
	Number	%	Number	%
Total	*259*	*100.0*	*938*	*100.0*
Non-interviewed				
Deceased	50	19.3	—	—
Inadequate address	19	7.3	—	—
Absent	1	0.4	32	3.4
Refused	9	3.5	21	2.2
Too ill	1	0.4	—	—
Other	5	1.9	15	1.6
Interviewed	*174*	*67.2*	*870*	*92.8*
Exclusions				
Age out of range	3	1.2	42	4.5
Previous mastectomy	—	—	2	0.2
Subjects in analysis	*171*	*66.0*	*826*	*88.3*

TABLE II - SELECTED CHARACTERISTICS OF BREAST CANCER CASES AND CONTROLS

Selected characteristics	Cases	Controls[1]
(N)	(171)	(826)
Mean age (years)	45.5	45.5
% in San José	46.8	35.4
% outside Central Valley	21.6	32.6
Mean years of education	6.5	5.2
% high economic level	40.4	26.6
% post-natural menopausal status	22.8	30.4
Mean age at menarche (years)	13.4	13.6
Mean stated weight at interview (kg)	61.5	61.1
% with 5 or more breast exams before 1982	21.6	12.5
% with "frequent" breast self-exams before 1982	20.5	14.6
% with fertility problems diagnosed	3.5	1.9
% ever smoked 100 or more cigarettes	22.2	21.2
% with family history of breast cancer	7.4	5.2
% with benign breast disease history	8.5	3.4
% ever used oral contraceptives	35.7	32.0
% ever used DMPA	11.7	6.0
Mean parity	3.8	5.1
Mean months of breast-feeding[2]	24.7	35.2
Mean age at first birth[2]	22.6	22.1
Mean birth recency (years)[2]	14.2	12.4
Mean months birth interval[2]	40.3	32.9

[1]Direct standardization to age structure of breast cancer cases, 5-year age groupings used.–[2]Parous women only.

We defined 5 fertility-related variables for each woman's reproductive history, taking into account only completed pregnancies—those with at least 6 months of gestation. *Parity*, or the number of completed pregnancies, was our most important variable. To clarify whether birth timing is associated with breast cancer independently of parity, we defined 3 additional variables, namely: *age at first completed pregnancy* or, in short, age at first birth; *birth recency* or the interval between last completed pregnancy and index date; and *mean birth interval*, which is the average of intervals between successive completed pregnancies. Duration of *breast-feeding*, defined as the total number of months of lactation for each woman, was also included as an independent variable.

The relative risk of breast cancer was estimated by the odds ratio, simultaneously adjusted for potential confounding effects with logistic regression methods (Schlesselman, 1982; Harrel, 1983). We included as confounders those variables that showed differences between cases and controls (Table II) and, at the same time, were correlated (correlation coefficient greater than 0.15) with at least one of the 5 fertility-related variables (Table III).

Since controls were selected to be frequency-matched to the age distribution of the combined group of cervical and breast cancer cases, the controls were younger on average than breast cancer cases (Lee *et al.*, 1987). To control the confounding effect of age in the model, we included 3 variables: years of age, a dummy variable to distinguish women younger and older than 44, and the product of these 2 variables. In this way, we adjusted for oversampling of older women. Other confounders included in our regression models were education (years), residence (San José, other), and menopausal status

TABLE III - CORRELATION COEFFICIENT BETWEEN REPRODUCTIVE FACTORS AND POTENTIAL CONFOUNDERS IN THE SAMPLE OF CONTROLS

Reproductive variables	Parity	Months of breast-feeding	Age at first birth	Birth recency	Birth interval
(N)	(825)	(741)	(744)	(742)	(657)
Parity	1.0	0.59	−0.47	−0.03	−0.42
Months of breast-feeding	0.59	1.00	−0.36	−0.10	−0.18
Age at first birth	−0.47	−0.36	1.00	−0.10	−0.01
Birth recency	−0.03	−0.10	−0.10	1.00	−0.24
Mean birth interval	−0.42	−0.18	−0.01	−0.24	1.00
Potential confounders					
Age	0.46	0.31	0.17	0.73	−0.14
Residence	−0.19	−0.13	0.07	0.09	0.15
Years of education	−0.39	−0.31	0.28	−0.11	0.18
Economic status	−0.31	−0.29	0.15	0.11	0.19
Age at menarche	−0.00	0.07	0.13	0.12	−0.10
Menopausal status	0.12	0.09	0.07	0.45	−0.05
Weight	0.09	0.02	−0.05	0.04	0.01
MD breast exams	−0.12	−0.12	0.05	0.02	0.08
Breast self-exams	−0.11	−0.08	0.01	−0.01	0.08
Fertility problems	−0.07	−0.07	0.02	0.01	0.08
Smoking (pack-years)	0.04	0.04	−0.08	0.13	0.04
Family history of breast cancer	0.00	0.03	−0.02	0.03	0.03
Benign breast disease	−0.09	−0.07	0.06	0.05	−0.05
OC use	−0.05	−0.09	0.02	−0.28	0.12
DMPA use	0.03	0.01	−0.03	0.08	0.00

Note: Coefficients were calculated with the sample of controls adjusted to the age structure of breast cancer cases.

(natural menopause, other). Controlling for the effect of these variables was sufficient to account for confounding by economic status.

To estimate the relative risks, we considered the fertility-related variables categorically. However, we also studied them as continuous variables to determine if a log-linear "trend" in their relationship with breast cancer existed. We used χ^2 statistics to test the association of variables in their continuous form (Schlesselman, 1982).

RESULTS

In a preliminary analysis performed separately for each reproductive factor, we found that all of these factors are significantly associated with the risk of breast cancer (Table IV).

Nulliparous women had a more than 2-fold increase in their risk of breast cancer compared with all parous women, and a 70% greater risk when compared with women with one or two completed pregnancies. We excluded nulliparous women from the rest of the reproductive history analysis.

For parous women, we found the expected negative association between breast cancer and increasing parity. Those women with 8 or more pregnancies showed a risk less than half that for women with 1 or 2 pregnancies. The pattern of decrease was statistically significant ($\chi^2 = 6.7$, $p < 0.05$), and the relative risk diminished by 9% on average for each additional completed pregnancy (data not shown).

The number of months of breast-feeding was also negatively associated with breast cancer. However, this association was weaker than that observed for parity. The relative risk diminished only after 12 months of lactation, with an average decrease in the risk of 8% for each additional 12 months of lactation ($\chi^2 = 4.6$, $p < 0.05$).

Age at first completed pregnancy showed a curvilinear association with breast cancer. Women who reported having their first child between 20 and 24 years of age had a 60% higher risk than women who began having children earlier. But after 25 years of age, the relative risk of cancer tended to decrease.

TABLE IV - THE RELATIVE RISK OF BREAST CANCER BY REPRODUCTIVE FACTORS

Reproductive factors	Cases N=171	Controls N=826	Relative risk[1]	(95% Confidence interval)
A. All women:				
Parity				
Nulliparous	29	81	2.1	(1.3–3.6)
Parous	142	744	1.0	(Referent)
Nulliparous	29	81	1.7	(0.9–3.0)
Parity 1–2	41	224	1.0	(Referent)
B. Parous women only:				
Parity				
1–2	41	224	1.0	(Referent)
3–4	48	217	0.9	(0.6–1.5)
5–7	31	172	0.5	(0.3–0.9)
8+	22	131	0.4	(0.2–0.8)
Trend (continuous)			$\chi^2=6.7$	($p=0.01$)
Breast-feeding (months)				
Less than 1	20	82	1.0	(Referent)
1–11	44	218	1.1	(0.6–2.0)
12–35	41	240	0.7	(0.4–1.3)
36+	37	201	0.6	(0.3–1.3)
Trend (continuous)			$\chi^2=4.6$	($p=0.03$)
Age at first birth				
Less than 20	35	286	1.0	(Referent)
20–24	69	289	1.6	(1.0–2.6)
25–29	27	118	1.2	(0.7–2.2)
30+	11	51	1.0	(0.4–2.1)
Trend (continuous)			$\chi^2=0.0$	($p=0.85$)
Birth recency				
0–9 years	48	434	1.0	(Referent)
10–19 years	58	253	0.9	(0.6–1.5)
20+ years	36	55	2.2	(1.1–4.4)
Trend (continuous)			$\chi^2=4.3$	($p=0.04$)
Mean birth interval				
8–23 months	33	217	1.0	(Referent)
24–35 months	39	210	1.2	(0.7–1.9)
36+ months	51	230	1.6	(0.9–2.6)
Trend (continuous)			$\chi^2=5.4$	($p=0.02$)

[1] Relative risk adjusted for age, residence, education, and menopausal status.

The risk of breast cancer more than doubled when 20 years or more had elapsed since the last pregnancy. However, if less time had elapsed, no effect of birth recency was observed.

Table IV also indicates a positive association between mean birth interval and breast cancer when the variable is considered in both categorical and continuous forms. The relative risk increases by an average of 1% for each additional month of mean birth interval.

Because the variables considered for reproductive history are correlated (Table III), we performed further analyses to establish whether the estimated associations from this preliminary analysis are independent.

Independence of effects

Table V depicts the relative risk of each of the 5 reproductive factors when each is controlled for the other 4, one at a time. The last column in the Table contains the risk estimate for each reproductive variable, except birth interval, when adjusted simultaneously for the other 3.

When the effect of parity was controlled for, neither breast-feeding, age at first birth, nor birth interval was significantly associated with breast cancer (second column of Table V). Most of the effect originally observed for these variables was only a reflection of the effect of parity. In contrast, parity and birth recency appear to have independent effects on breast cancer risk.

For a woman of a specific age, 3 of the 4 variables—parity, age at first birth, birth recency, and mean birth interval—automatically define the fourth. Because of this problem of multi-colinearity, we cannot construct a model that includes all 4 variables in the same regression. Since mean birth interval did not demonstrate an association independent of parity, we discarded it in all subsequent analyses. The net or independent association was therefore estimated by including all 4 factors, except birth interval, in the final model. Results of the multivariate analysis are shown in the last column of Table V. In addition to low parity, only 20 or more years of birth recency was a significant risk factor for breast cancer.

Interaction

To determine whether the observed relationships differed between subgroups, we examined the 2-factor interactions between each reproductive history variable and each confounder. There were statistically significant interactions only with age and residence. The only risk factor for breast cancer before the age of 45 years was nulliparity (Table VI). In contrast, nulliparity did not demonstrate any effect after age 45 when a protective effect of high parity emerged. Among women younger than 45, the nulliparous women showed a risk of breast cancer that was triple that of parous women. Among women older than 45, the risk decreased by an average of 13% with each additional pregnancy. Because of the small number of observations, we do not know whether the differences by age observed in Table VI for the rest of the reproductive variables are genuine or should be attributed to chance.

Table VI also contains a comparison of the estimates for San José with those of the rest of the country. In San José, where data presumably are more reliable, the protective effect of parity persisted. In addition, an independent effect of lactation appears for the first time in this data set. Similar patterns were seen in women with higher educational levels and higher economic status (not shown).

Further analysis of interactions between the variables of reproductive history identified 2 interactions of some importance: between parity and age at first birth, and between parity and birth recency. The 2 variables of birth timing appear to be associated with breast cancer only for lower parity women, especially in older women (Table VII).

Among parous women aged 45 and older, the risk of breast cancer was much higher in the group that began having children between 20 and 24 years of age and had had fewer than 5 pregnancies. This subgroup, which contains only 25 cases and 13 controls, showed a relative risk of 7.9 with reference to the women with high parity and having had their first child before the age of 20. The elevated risk for older women with fewer than 5 pregnancies and for whom 20 or more years had passed since their last pregnancy is also worth noting. This

TABLE V – THE RELATIVE RISK OF BREAST CANCER IN PAROUS WOMEN BY REPRODUCTIVE FACTORS ACCORDING TO SEVERAL ADJUSTMENTS

Reproductive factors	Relative risk[3] additionally adjusted by						
	None	Parity	Breast-feeding	Age at first birth	Birth recency	Birth interval	All other[4]
Parity							
1–4 (Referent)	1.0	—	1.0	1.0	1.0	1.0	1.0
5+	0.5[1]	—	0.6[1]	0.4[1]	0.6[1]	0.6[1]	0.6[1]
(Continuous: χ^2)	(6.7)[1]	—	(2.7)	(9.0)[1]	(3.9)[1]	(3.1)	(3.3)
Breast-feeding							
< 12 months (Referent)	1.0	1.0	—	1.0	1.0	1.0	1.0
12+ months	0.6[1]	0.8	—	0.6[1]	0.7	0.7	0.8
(Continuous: χ^2)	(4.6)[1]	(1.0)	—	(5.3)[1]	(2.9)	(3.8)	(1.4)
Age at first birth							
< 20 (Referent)	1.0	1.0	1.0	—	1.0	1.0	1.0
20–24	1.6[1]	1.5	1.6[1]	—	1.7[1]	1.6[1]	1.6
25+	1.1	0.8	1.0	—	1.2	1.0	0.9
(Continuous: χ^2)	(0.0)	(2.4)	(0.9)	—	(0.2)	(0.2)	(1.9)
Birth recency							
< 20 years (Referent)	1.0	1.0	1.0	1.0	—	1.0	1.0
20+ years	2.4[1]	2.0[1]	2.3[1]	2.4[1]	—	2.4[1]	1.8[1]
(Continuous: χ^2)	(4.3)[1]	(1.0)	(2.2)	(4.4)[1]	—	(3.0)	(1.0)
Mean birth interval							
< 36 months (Referent)	1.0	1.0	1.0	1.0	1.0	—	—[2]
36+ months	1.5	1.2	1.4	1.5	1.6[1]	—	—[2]
(Continuous: χ^2)	(5.4)[1]	(2.5)	(4.2)[1]	(5.5)[1]	(7.2)[1]	—	—[2]

[1]Relative risk significantly different from 1 (when continuous beta different from 0) at $p < 0.05$.–[2]Variable not included in the model, since it is completely defined by parity, age at first birth, and birth recency.–[3]Odds ratio adjusted for age, residence, education, menopausal status, and the variables in that column.–[4]The column labelled "All other" displays the risk estimates for each factor, except birth interval, when adjusted simultaneously for the other 3 reproductive factors.

TABLE VI - RELATIVE RISK[1] OF BREAST CANCER BY REPRODUCTIVE FACTORS, STRATIFIED BY AGE AND RESIDENCE

Variable	Total	Age		Residence	
		<45	45+	San José	Other
(N cases)	(171)	(74)	(97)	(80)	(91)
(N controls)	(826)	(549)	(277)	(284)	(542)
A. All women					
Motherhood					
Nulliparous	2.1[2]	3.2[2]	1.4	2.2[2]	2.4[2]
Parous (Referent)	1.0	1.0	1.0	1.0	1.0
Nulliparous	1.7[2]	3.1[2]	0.8	2.0	1.8
Parity 1–4 (Referent)	1.0	1.0	1.0	1.0	1.0
B. Parous women only					
(N cases)	(142)	(57)	(85)	(66)	(76)
(N controls)	(744)	(492)	(252)	(251)	(493)
Parity					
1–4 (Referent)	1.0	1.0	1.0	1.0	1.0
5+	0.6[2]	1.2	0.3[2]	0.4[2]	0.7
(Continuous: χ^2)	(3.3)[2]	(0.3)	(5.2)[2]	(5.4)[2]	(0.4)
Breast-feeding					
<12 months (Referent)	1.0	1.0	1.0	1.0	1.0
12+ months	0.8	0.6	0.9	0.5[2]	1.2
(Continuous: χ^2)	(1.4)	(1.1)	(0.4)	(0.1)	(0.7)
Age at first birth					
<20 (Referent)	1.0	1.0	1.0	1.0	1.0
20–24	1.6	1.4	2.0[2]	1.7	1.5
25+	0.9	1.4	0.6	0.7	1.1
(Continuous: χ^2)	(1.9)	(0.1)	(3.0)	(2.5)	(0.2)
Birth recency					
<20 years (Referent)	1.0	1.0	1.0	1.0	1.0
20 + years	1.8[2]	3.0[3]	1.5	1.8	2.0
(Continuous: χ^2)	(0.0)	(0.4)	(0.1)	(0.6)	(0.2)

[1]Odds ratio adjusted for age, residence, education, menopausal status, and in parous women, for parity, breast-feeding, age at first birth, and birth recency.–[2]Relative risk significantly different from 1.0 at $p<0.05$ level.–[3]Less than 10 cases.

TABLE VII - RELATIVE RISK OF BREAST CANCER, ADJUSTED FOR REPRODUCTIVE FACTORS: INTERACTION BETWEEN PARITY AND AGE AT FIRST BIRTH AND BETWEEN PARITY AND BIRTH RECENCY—PAROUS WOMEN ONLY

Variable	N Cases/Controls		Relative Risk[1]	
	Parity 1–4	Parity 5+	Parity 1–4	Parity 5+
A. Parous women, all ages				
Age at first birth				
<20	11/126	24/160	0.9	1.0 (Ref.)
20–24	44/172	25/117	2.6[2]	1.0
25+	34/143	4/26	1.2	(0.7)
Birth recency				
<20 years	59/408	47/281	1.4	1.0 (Ref.)
20+ years	30/33	6/22	3.7[2]	(0.9)
B. Parous women, age 45+				
Age at first birth				
<20	6/16	13/74	(1.5)	1.0 (Ref.)
20–24	25/13	19/75	7.9[2]	1.3
25+	19/51	3/23	1.4	(0.8)
Birth recency				
<20 years	22/51	29/150	2.7[2]	1.0 (Ref.)
20+ years	28/29	6/22	5.2[2]	(1.0)

[1]Relative Risk=Odds ratio adjusted for age, residence, education, and menopausal status. Model also included adjustments for all reproductive factors (parity, breast-feeding, age at first birth, and birth recency). Estimates are in parentheses if based on less than 10 cases.–[2]Relative risk significantly different from 1.0 at $p<0.05$ level.

group showed a breast cancer risk more than 5 times greater than that for older women with high parity and less than 20 years since their last pregnancy (Table VII).

DISCUSSION

The relationship between reproductive history and breast cancer has been analyzed for the first time in a population with high fertility. In one previous study, performed in São Paulo, Brazil, 33% of the controls had a parity of 5 or more (Mirra *et al.*, 1971). In the current study, 50% of the controls (adjusted to the age distribution of the cases) reported a parity of 5 or more. Because of this, the results obtained here may not be strictly comparable with those reported in earlier studies.

We found that the risk of breast cancer is higher for nulliparous women. However, this effect is statistically significant

TABLE VIII - PERCENT DISTRIBUTION BY PARITY AND AGE AT FIRST BIRTH IN 1976 FOR THE CONTROL GROUP AND FOR WOMEN INTERVIEWED IN THE 1976 WORLD FERTILITY SURVEY

Variables (status in 1976)	Women 20–34 years in 1976		Women 35–49 years in 1976	
	WFS[1]	Controls[2]	WFS[1]	Controls[2]
(N)	(2,478)	(421)	(1,457)	(342)
Total	*100.0*	*100.0*	*100.0*	*100.0*
Parity				
0	29.3	27.0	9.7	8.4
1–3	51.7	53.6	23.7	25.7
4+	19.1	19.4	66.6	66.0
(Mean parity)	(2.0)	(2.0)	(5.7)	(5.5)
Age at first birth				
Parous women only				
<20	47.8	46.4	37.5	37.6
20–24	41.6	40.8	42.6	36.9
25+	10.7	12.7	19.9	25.5
(Mean age)	(20.1)	(20.2)	(21.4)	(21.9)

[1]Unpublished tabulations from World Fertility Survey.–[2]Figures adjusted to October, 1976, and age-adjusted for oversampling.

only in those women under 45 years of age. This finding is in contrast to the American nurses cohort study which found that nulliparity was associated with low breast cancer risk in younger women (Pathak *et al.*, 1986). We also found that higher parity has a significant protective effect, which is independent of the duration of breast-feeding, age at first completed pregnancy, and recency of last pregnancy.

This study demonstrated no significant independent association of birth spacing. Moreover, the association between duration of lactation and breast cancer was statistically significant when adjusted for the effect of parity, but only for residents of San José. This is consistent with recent, well-controlled studies in developed countries (Lubin *et al.*, 1982; Byers *et al.*, 1985; McTiernan and Thomas, 1986). However, breast-feeding practices in Costa Rica differ from those in many developing countries. For example, the mean duration of breast-feeding in Costa Rica is 9.3 months, compared to 18.0 months in Guatemala (Rosero-Bixby *et al.*, 1987).

The curvilinear relationship between age at first completed pregnancy and breast cancer is different from that observed in other populations, where the risk increases uniformly with age at first birth. This curvilinear association may be a peculiarity of the study population, but may also be spurious, due to errors in reporting the date of first pregnancy. To assess the possibility of recall error, we compared the distribution of age at first birth for the control group with that of the World Fertility Survey of 1976, a national sample survey. An important discrepancy among older women emerges (Table VIII). Substituting the distribution of age at first birth observed in the 1976 survey for the distribution of the current study's controls eliminated the curvilinear pattern (data not shown). In retrospective surveys, older women frequently report events from the distant past, such as marriage or first birth, as occurring later than they actually did. This problem has been attributed to difficulties in recall for older women and a tendency to omit a first child who subsequently died (Goldman *et al.*, 1985).

There was a positive association between the time since last completed pregnancy and breast cancer, but the effect of this variable appears only after an interval of 20 years or more. This pattern is consistent with a prolonged latent period of breast cancer. However, if the influence of age at first birth was distorted by recall errors, then the effect of birth recency may also have been distorted by this type of problem.

Both age at first birth and recency of last birth showed an interaction with parity. Their effect on risk of breast cancer appeared only in women with low parity, and the protective effect of high parity occurred primarily when the risk attributable to the other two variables was higher. Because of these interactions, differentiation between the effects of the distinct factors of reproduction is difficult.

The population-based study design of the present study eliminates some of the methodological problems in control selection that are common in hospital-based studies. However, selection bias may have affected the cases available for interview. The coverage of breast cancer screening programs in Costa Rica varies by age, region, and socio-economic status (Lee *et al.*, 1987). In addition, interviews were not completed for a third of the cases diagnosed during the 25-month eligibility period, chiefly because 19% of the patients had died before the interview period began. Based on information in the tumor registry, cases not interviewed were slightly more likely to have been diagnosed in 1982, to be from San José, and to have an unspecified tumor type (Lee *et al.*, 1987). The non-interviewed cases were less likely to have a telephone number listed in their hospital record, suggesting that these cases may have had a lower socio-economic status. An additional problem in the study design may prove to be an association between the woman's reproductive history and possible deficiencies in the coverage of the Tumor Registry. However, an analysis restricted only to the population of San José, where ascertainment of cases is probably nearly complete, resulted in conclusions similar to those from the national analysis, with the exception that breast-feeding appeared to have a protective effect. A previous study showed that the Costa Rican Tumor Registry had captured most gynecological cancer cases diagnosed since 1980 (Rosero-Bixby and Grimaldo, 1987).

The present study agrees with other recent investigations that have found an independent effect of parity in developed countries (Layde *et al.*, 1986; Helmrich *et al.*, 1983). Clearly, identifying independent effects of reproductive factors is important to better understand the etiology of breast cancer. However, from the public health standpoint, a precise differentiation of the independent effects may be of little importance, because changes in different aspects of reproductive behavior often occur simultaneously. On the other hand, strong risk factors may be of little importance from a public health standpoint if they are infrequent and, therefore, have a low attributable risk.

The results of the present study were extrapolated to evaluate the impact of fertility decline on the trends of breast cancer in Costa Rica. Only the effect of changes in parity was consid-

TABLE IX - PROJECTION OF BREAST CANCER INCIDENCE IN COSTA RICA TO YEAR 2000, ACCORDING TO PREDICTED CHANGES IN FERTILITY

Age	Percent nulliparous[1]		Mean parity[2]		Breast cancer incidence/100,000		
	1980	2000	1980	2000	Observed 1980-83[3]	Projections 2000[4] A	B
30-34	10	16	3.05	2.42	9	8	9
35-39	9	14	4.22	2.91	25	25	26
40-44	8	12	5.41	3.22	45	54	57
45-49	8	10	6.28	3.44	77	113	115
50-54	8	8	6.70	3.81	89	123	123
55-59	8	8	7.02	4.55	96	120	120
Average 30-59	*8.5*	*11.3*	*5.45*	*3.39*	*57*	*74*	*75*

[1]Proportion estimated for 1980 based on data from census of 1973 and fertility surveys of 1976 and 1981. Projection to year 2000 made by authors assuming increase in nulliparity.-[2]Mean parity estimated for 1980 based on age-specific fertility rates for the period 1950-1980, and for year 2000 based on official median projection (DGEC and CELADE, 1983).-[3]Rates from National Tumor Registry (Rosero-Bixby and Grimaldo, 1987).-[4]Projections based on models of logistic regression with adjustment for age, residence, education and menopausal status, and with interaction between age and parity. Hypothesis "A" assumes changes only in parity. Hypothesis "B" assumes changes in both parity and proportion nulliparous.

ered because that factor reflects much of the variation of the other reproductive factors.

The steep decline in Costa Rican fertility had practically no effect on past trends of breast cancer because the affected cohorts have not entered the peak years of breast cancer incidence. However, the situation will change in coming years. Between the years 1980 and 2000, completed fertility will decline by an average of almost 3 children for women aged 45 to 59 (Table IX). Combining this reduction with the relative risks estimated for parity as a continuous variable, we have projected breast cancer incidence in the year 2000. This simplistic exercise resulted in a 30% mean increase in breast cancer incidence over the 1980-83 rates for women between 30 and 59 years of age. This expected increase was concentrated in women around 50 years of age (Table IX, Projection A—about 40%). In a second projection, assuming a decrease in parity and an increase in nulliparity, the result was similar to the first projection (Table IX, Projection B). Thus, although nulliparity is an important risk factor, it will probably not influence Costa Rica's breast cancer trends. In contrast, the decline in parity could eventually contribute to an increase in breast cancer rates in Costa Rica.

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