A Case-Control Study of Breast Cancer and Hormonal Contraception in Costa Rica [1,2,3]

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ABSTRACT—By 1981, 11% of married women in Costa Rica ages 20-49 years had used depot-medroxyprogesterone acetate (DMPA) and 58% had used oral contraceptives (OCs). Since 1977, the Costa Rican Ministry of Health has maintained a nationwide cancer registry. These circumstances provided an opportunity for a population-based, case-control study of DMPA, OCs, and breast cancer in Costa Rica. Cases were 171 women ages 25-58 years with breast cancer diagnosed between 1982 and 1984; controls were 826 women randomly chosen during a nationwide household survey. Cases and controls were interviewed with the use of a standard questionnaire covering their reproductive and contraceptive histories. Logistic regression methods were used to adjust for confounding factors. While few cases or controls had ever used DMPA, DMPA users had an elevated relative risk (RR) estimate of breast cancer of 2.6 (95% confidence limits=1.4-4.7) compared with never users. However, no dose-response relationship was found; even the group of women who had used DMPA for less than 1 year had an elevated RR estimate (RR=2.3; 95% confidence limits=1.0-5.1). In contrast, OC users had no elevation in RR compared with never users (RR=1.2; 95% confidence limits=0.8-1.8). The results of the DMPA analysis are inconclusive. Before decisions are made on whether to continue providing this effective contraceptive method, other ongoing studies will need to confirm of refute these findings.—JNCI 1987; 79:1247-1254.

Approximately 2 million women worldwide currently use injectable DMPA for contraception (*1*). Although DMPA has yet to be directly linked to any human cancer, the possibility of such an association, especially with breast cancer, was one of the reasons the U.S. Food and Drug Administration denied approval of DMPA for contraceptive use in the United States (*2*). Because of concern about the failure to obtain such approval, many governments in recent years have withheld or withdrawn approval of DMPA. Because DMPA has been used in Costa Rica for more than 15 years and OC use is widespread, Costa Rica offers an opportunity to examine the relationship between use of hormonal contraceptives and the development of breast and cervical cancers.

Costa Rica has one of the highest prevalences of contraceptive use in Latin America; 65% of currently married women 15-49 years of age reported currently using a contraceptive method in 1981 (*3*). DMPA was first used as a contraceptive method in Costa Rica around 1970, although it was not licensed for general distribution until 1973. By 1981, 11% of currently married women reported ever use of an injectable form of contraception, most of which was DMPA. OCs were introduced in Costa Rica in the early 1960's. They remain the most commonly used form of contraception. By 1981, 58% of currently married women reported ever use of OCs (*3*).

In 1970 cancer was the fourth leading cause of death in Costa Rica but has recently moved to second place (*4*). Among Costa Rican women, deaths related to breast cancer have gradually increased to reach a mortality rate of 13 per 100,000 in 1983 (*5*). The yearly incidence of breast cancer in Costa Rican women older than 20 years of age is about 39 per 100,000 women. The incidence of breast cancer in U.S. white women tends to be two to three times higher than in Costa Rican women of the same age.

In 1984 the Costa Rican Demographic Association conducted a nationwide, population-based, case-control study of breast and cervical cancers in collaboration with the Division of Reproductive Health at the Centers for Disease Control. Additional assistance was received from the Costa Rican Ministry of Health, the Costa Rican Social Security System, and Family Health International. In this report we present results from analyses of the association between breast cancer and use of hormonal contraceptives.

ABBREVIATIONS USED: DMPA=depot-medroxyprogesterone acetate; OC=oral contraceptive; RR=relative risk; WHO=World Health Organization.

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SUBJECTS AND METHODS

Cases.—Since 1977 the Costa Rican Ministry of Health has maintained a nationwide cancer registry (*4*). Since 1980 all hospitals and private pathologists have agreed to report to the registry any hospitalizations or outpatient biopsies associated with a cancer diagnosis. Death certificates and autopsy reports have provided additional sources of information. We examined the completeness of reporting to the cancer registry by linking a sample of gynecologic cancer cases from the 1983 Costa Rican National Hospital Discharge Summary to the cancer registry files. The registry contained information on 130 of the 133 (97.7%) hospital discharges in the sample. The registry does not obtain information on cancer cases who obtain their diagnosis and treatment outside of the country, although these are thought to represent a small proportion of cancers developing in Costa Ricans.

To decrease the time required for data collection, we elected a method of retrospective enrollment of cancer cases. From the National Tumor Registry records, we chose all women with breast or cervical cancer, newly diagnosed between January 1, 1982, and March 31, 1984, who were 25-58 years of age at the time of diagnosis. From these records, 256 women were eligible for enrollment as breast cancer cases.

Controls.—Because the cases were ascertained from a population-based registry, we chose a population-based method to select the control group. We used a multistage, probability household survey throughout Costa Rica to select controls, at which time cases and controls were interviewed. The survey and interviews were conducted between September 1984 and February 1985. The sampling frame used for the survey was based on maps and preliminary results from the June 1984 census. A nationwide sample of census sectors had been selected at random before the survey began. Each sector contained approximately seven households. From these households, all women 25-59 years of age at the time of survey were eligible to be selected as controls. In the final control selection, women in older age groups were oversampled so that the age distribution of the controls would be frequency matched to the age distribution of the combined group of all cancer cases in the study. During the survey, 938 women were selected as potential controls.

Interviews.—Cases and controls were interviewed in their homes with the use of a standard questionnaire modified from the Cancer and Steroid Hormone Study (*6*). The interviews were conducted by female interviewers who had undergone a week-long training course. The interviews lasted about 45 minutes and gathered extensive information concerning the women's reproductive, medical, and sexual histories. A calendar of life events was used to assist recall of contraceptive use up to the time of interview (*6*).

If a woman reported having used OCs, but had never used them for at least 3 consecutive months, dates of her OC use were not recorded. If a woman reported ever using an injectable contraceptive, she was asked the type of injection. Only if she specifically reported use of DMPA or a 3-month injectable contraceptive was she considered to have used DMPA.

Only 66.8% of the eligible breast cancer cases were interviewed (table 1); death was the major reason that women eligible to be cases were not interviewed (19.5%). The interview completion rate among women selected to be controls was 92.8%.

Using data from the tumor registry, we compared the breast cancer cases who were interviewed with those who were not interviewed. Cases not interviewed were slightly more likely to have been diagnosed in 1982, to be younger, to be from San Jose, and to have an unspecified tumor type; the noninterviewed cases were less likely to have access to a telephone (25.9% compared with 32.7%), suggesting that, as a group, they may have had a lower socioeconomic status.

We assessed the representativeness of the interviewed controls by comparing them with a nationwide sample of women obtained during two recent surveys. The age distribution of the interviewed controls, after adjustment for oversampling, was similar to the expected age distribution based on the 1984 census. Furthermore, the distribution of controls by education, marital status, and contraceptive use closely matched the distribution reported in a 1981 survey (*3*).

Definitions.—Because of the retrospective enrollment of the case group, we established before data analysis began an *index date* to ensure that exposures and other events that occurred after this date were not included in our analyses. For a case, the index date was her date of diagnosis recorded by the cancer registry; for a control, the index date was February 15, 1983, the halfway point in the 27-month period of case eligibility. We had information available so that the following variables used in this analysis could be adjusted for index date: all variables characterizing DMPA and OC exposure, age, parity, history of benign breast disease, menopausal status, history of breast-feeding, and age at first full-term pregnancy.

For each woman who reported ever using DMPA or using OCs for at least 3 consecutive months, we used information from the life calendar to characterize and quantify her hormonal contraceptive usage, up to her index date. We determined: 1) *duration of use*—total months of use, whether intermittent or continuous (one injection of DMPA was considered to provide 3 mo of

TABLE 1.—*Interview outcome for breast cancer cases and controls*

Interview outcome	Cases		Controls	
	No.	Percent	No.	Percent
Completed	171	66.8	870	92.8
Refused	9	3.5	21	2.2
Deceased	50	19.5	—	—
Unknown address	19	7.4	—	—
Not at home	1	0.4	32	3.4
Other	6	2.3	15	1.6
Total	256		938	

use); 2) *time since first use*—number of months since first use; 3) *time since last use*—number of months since last use; and 4) *age at first use*. If a woman did not know all her dates of use, unknown values were assigned to the above variables. If a woman reported using DMPA or OCs, but the first use of the method occurred after her index date, she was considered to have never used the method.

Using a method developed at the University of Costa Rica, we assigned a *socioeconomic status index* ranging from 0 to 17, based on the reported possession of 8 major household appliances. A woman had a *history of benign breast disease* if she reported breast surgery for a biopsy of a cyst or lump that did not result in a mastectomy. A woman had a *first-degree family history of breast cancer* if she reported that her mother, sister, or daughter had a history of breast cancer.

Analysis.—We excluded from the control group 42 women whose ages at index date were not between 25 and 58 years and 2 women who reported previous mastectomies. This left 171 cases and 826 controls available for the breast cancer analysis.

We used logistic regression models (*7, 8*) containing the exposure of interest (either DMPA or OC use) and age at index date to control individually for the following potentially confounding factors: education, geographic region of residence, socioeconomic status index, marital status, weight, parity, menopausal status, use of OCs, use of DMPA, history of benign breast disease, age at first full-term pregnancy, history of breast-feeding, self-reported history of infertility, first-degree family history of breast cancer, and reported number of breast examinations by a physician or nurse before 1982. The following variables were found to distort the risk estimates associated with one or both exposures: age, parity, region of residence, socioeconomic status index, marital status, menopausal status, history of breast-feeding, age at first full-term pregnancy, and DMPA use (in the OC analysis). The final logistic regression models contained age (as a continuous variable), parity (continuous), socioeconomic status index (continuous), and DMPA use (ever, never), since simultaneously controlling for these factors eliminated the confounding effects produced by the other variables.

RESULTS

Table 2 presents various demographic and reproductive characteristics of the breast cancer cases and controls. Recall that controls were selected to be frequency matched to the age distribution of the combined group of cervical and breast cancer cases. Because the cervical cancer case group was substantially younger than the breast cancer case group, the controls were younger than the breast cancer cases. Therefore, we present the percent distribution of characteristics of the control group standardized to the age distribution of the breast cancer case group. Compared with controls, a greater proportion of breast cancer cases had a high socioeconomic status and education level, lived in the capital city of

TABLE 2.—*Percent distribution of characteristics of breast cancer cases and controls*

Characteristic	Percent distribution	
	Cases (n=171)	Controls (n=826)
Age at index date, yr		
25-34	9.9	37.3
35-39	14.0	15.6
40-44	19.3	13.6
45-49	20.5	13.7
50-54	22.8	13.8
55-58	13.5	6.1
Region of residence[a]		
San Jose	46.8	35.3
Central Valley	31.6	32.0
Other urban areas	10.5	10.0
Other rural areas	11.1	22.7
Education, yr[a]		
<6	40.9	54.9
6	24.0	21.3
>6	35.1	23.7
Socioeconomic status index[a]		
Low (0-3)	29.8	43.6
Medium (4-8)	29.8	29.8
High (9-17)	40.4	26.6
Marital status[a]		
Currently married	54.4	62.0
Previously married	14.6	17.2
Cohabiting	6.4	5.3
Single	24.6	15.4
Parity[a]		
0	17.0	8.7
1-2	24.0	18.4
3-4	28.1	22.7
≥5	31.0	50.1
Unknown	0.0	0.1
Age at first full-term pregnancy, yr[a]		
Nulliparous	17.0	8.7
<20	20.5	32.9
20-24	40.3	34.1
25-29	15.8	15.9
≥30	6.4	8.3
Unknown	0.0	0.1
History of benign breast disease[a]		
No	87.7	96.5
Yes	8.2	3.5
Unknown	4.1	<0.1
Family history of breast cancer[a]		
No	87.7	88.8
Yes	7.0	5.1
Unknown	5.3	6.1
Menopausal status[a]		
Premenopausal	67.8	62.4
Post-natural	22.8	29.3
Post-surgical	8.8	8.1
Unknown	0.0	0.2
Ever breast fed?[a]		
Nulliparous	17.0	8.7
No	11.7	9.6
Yes	71.3	81.2
Unknown	0.0	0.6
No. of breast examinations by a health provider before 1982[a]		
0	51.5	54.0
1-4	26.9	33.0
5-9	6.4	5.2
≥10	15.2	7.3
Unknown	0.0	0.5

[a] Distribution of the control group standardized to the age distribution of the case group.

TABLE 3.—*Duration of DMPA use by breast cancer cases and controls*[a]

Duration of DMPA use	No. of cases	No. of controls	Odds ratio		95% confidence interval
			Crude	Adjusted[b]	
Never	129	724	1	1	Referent
Ever	19	49	2.2	2.6	1.4-4.7
<12 mo	9	30	1.7	2.3	1.0-5.1
12-23 mo	5	7	4.0	4.4	1.2-15.7
24-71 mo	5	8	3.5	3.4	1.0-11.0
≥72 mo	0	4	0	0	—

[a] Exclusions: 23 cases and 50 controls 55-58 yr old, 2 controls with unknown duration of DMPA use, and 1 control with unknown parity.
[b] Adjusted for age, parity, and socioeconomic status.

San Jose, were single, had low parity, and reported a history of benign breast disease.

DMPA Use and Breast Cancer Risk

Because only 1 case and no controls 55 years or older had ever used DMPA, we restricted the DMPA analysis to women 25-54 years of age. Although few cases or controls had ever used DMPA, we found that women who had ever used DMPA had a statistically significant elevated risk of breast cancer of 2.6 (95% confidence limits = 1.4-4.7) compared with women who had never used DMPA (table 3).

Any dose-response effect was difficult to evaluate because of the small number of DMPA users. However, we found no such relationship; i.e., there was no effect of increasing duration of DMPA use on breast cancer risk (table 3). Women who had used DMPA for less than 12 months had an elevated risk compared with never users, whereas the longest-term users had a risk estimate of zero.

The RR of breast cancer associated with DMPA use was highest for women who had the longest time since first use (table 4). Women who first used DMPA 10 or more years before the index date had a fourfold risk of breast cancer compared with never users. The risk of breast cancer associated with DMPA use was elevated regardless of the time since last use (table 4) or age at first use (not shown).

We found no important differences in the association between DMPA use and breast cancer among various subgroups of women (table 5). Women of various age, parity, and socioeconomic status levels all had elevated RR estimates. Insufficient numbers of DMPA users existed to examine the effects of OC use, history of benign breast disease, and family history of breast cancer on the DMPA-breast cancer association.

OC Use and Breast Cancer Risk

Compared with women who reported never using OCs, women who reported ever using OCs had a risk of developing breast cancer of 1.2 (0.8-1.8) (table 6). Note that women were excluded who had never used OCs for 3 or more consecutive months, since we could not be certain that any of that use had occurred before their index date. Women who had used OCs for a total duration of 36-59 months had an elevated RR estimate of 2.0 (1.0-4.1); women in other duration categories had no increased risk. Women with the longest duration of OC use had an RR of 1.0 (0.4-2.6). There were no effects of time since first or last OC use (table 7) or age at first OC use (not shown). Women who had first used OCs before the age of 25 had a risk of 0.9 (0.4-1.7) compared with never users.

A woman's age at index date did not affect the association between OC use and breast cancer (table 8). Nulliparous women had an elevated RR; however, there were only 3 cases and 3 controls who had ever used OCs in the nulliparous group.

TABLE 4.—*Time since first and last use of DMPA by breast cancer cases and controls*[a]

DMPA use	No. of cases	No. of controls	Adjusted odds ratio[b]	95% confidence interval
Never	129	724	1	Referent
Time since first use, yr				
<5	5	19	2.1	0.7-5.8
5-9	6	18	2.0	0.7-5.6
≥10	8	12	4.0	1.5-10.3
Time since last use, yr				
<5	8	26	2.2	1.0-5.2
≥5	11	23	2.9	1.3-6.5

[a] Exclusions: 23 cases and 50 controls 55-58 yr old, 2 controls with unknown time since first and last DMPA use, and 1 control with unknown parity.
[b] Adjusted for age, parity, and socioeconomic status.

TABLE 5.—*DMPA use and breast cancer risk by selected characteristics*[a]

Characteristic	Ever user		Never user		Adjusted odds ratio[b]	95% confidence interval
	No. of cases	No. of controls	No. of cases	No. of controls		
Age at index date, yr						
25-39	5	27	36	409	2.4	0.8-6.6
40-44	5	10	28	102	2.0	0.6-6.5
45-49	6	6	29	107	5.4	1.6-18.5
50-54	3	8	36	106	1.3	0.3-5.3
Parity						
0	2	1	25	74	2.9	0.2-38.8
1-2	3	9	32	210	2.1	0.5-9.0
3-4	5	20	35	187	1.7	0.6-5.0
≥5	9	21	37	253	3.4	1.4-8.2
Socioeconomic status						
Low	9	27	37	325	2.8	1.2-6.6
Medium	6	14	39	213	3.1	1.1-9.0
High	4	10	53	186	1.3	0.4-4.6
Region of residence						
San Jose	10	16	58	250	2.6	1.1-6.3
Central Valley-other urban areas	3	19	59	321	1.1	0.3-3.9
Other rural areas	6	16	12	153	5.4	1.7-17.0
No. of breast examinations						
0	10	24	65	373	2.6	1.1-6.1
1-2	5	11	18	171	4.0	1.2-13.3
≥3	4	16	46	177	1.4	0.4-4.5

[a] Exclusions: 23 cases and 50 controls 55-58 yr old and 1 control with unknown parity.
[b] In each characteristic stratum, ever users of DMPA are compared with never users. Each model includes age, parity, socioeconomic status, the variable of interest, and the appropriate interaction terms.

TABLE 6.—*Duration of OC use by breast cancer cases and controls*[a]

Duration of OC use	No. of cases	No. of controls	Odds ratio		95% confidence interval
			Crude	Adjusted[b]	
Never	97	427	1	1	Referent
Ever	58	321	0.8	1.2	0.8-1.8
<12 mo	13	72	0.8	1.2	0.6-2.4
12-35 mo	12	87	0.6	0.8	0.4-1.5
36-59 mo	14	52	1.2	2.0	1.0-4.1
60-119 mo	13	81	0.7	1.2	0.6-2.3
≥120 mo	6	29	0.9	1.0	0.4-2.6

[a] Exclusions: 13 cases and 67 controls without ≥3 consecutive mo of OC use, 3 cases and 10 controls with unknown duration of OC use, and 1 control with unknown parity.
[b] Adjusted for age, parity, socioeconomic status, and ever use of DMPA.

TABLE 7.—*Time since first and last use of OCs by breast cancer cases and controls*[a]

OC use	No. of cases	No. of controls	Adjusted odds ratio[b]	95% confidence interval
Never	97	427	1	Referent
Time since first use, yr				
<10	17	145	1.2	0.6-2.2
10-14	18	116	0.9	0.5-1.7
15-19	19	42	1.9	1.0-3.6
≥20	4	18	0.7	0.2-2.3
Time since last use, yr				
<5	20	172	1.1	0.6-2.0
5-9	18	82	1.1	0.6-2.1
≥10	20	67	1.2	0.7-2.2

[a] Exclusions: 13 cases and 67 controls without ≥3 consecutive mo of OC use, 3 cases and 10 controls with unknown time since first and last OC use, and 1 control with unknown parity.
[b] Adjusted for age, parity, socioeconomic status, and ever use of DMPA.

If ever use of DMPA were associated with an increased likelihood that breast cancer might be detected, our results could be biased in a positive direction. That the risk associated with DMPA use was lower for those women with more frequent breast examinations and with high socioeconomic status supports this possibility (*see* table 5). Table 10 presents the percentage of women in the control group who reported ever having a breast examination before 1982 performed by a health provider, stratified by ever use of hormonal contraceptives and by selected characteristics. Although fluctuations in the percentages occurred, there were no discernible patterns of differences between DMPA users and never users of DMPA in the percentage of women with breast examinations, by age, parity, region, or socioeconomic status. In contrast, OC users may have been more frequently screened than never users of OCs, especially among the older age groups and women of higher parity and socioeconomic status. Although hampered by the small number of DMPA users, the lack of major differences in the possibility of tumor detection between control users and nonusers argues that a detection bias in the DMPA analysis is unlikely to account for all the elevated RR found.

Inaccurate recall of DMPA use would result in a spurious increase in the RR only if there were differential misclassification, with cases incorrectly classified as DMPA users more often than controls. Nondifferential misclassification of the exposure generally should bias the RRs toward 1.0. The retrospective enrollment of the case group made classifying contraceptive exposure difficult because we were only interested in exposure before cancer diagnosis among cases and before February 15, 1983, among controls. Recall that the interviewers did not use the index date when collecting information from cases or controls; rather, contraceptive history up to the time of interview was collected from all women in the study. Breast cancer cases were interviewed up to 3 years after diagnosis; controls were interviewed about 18 months after the control group's index date. Use of a life calendar to obtain contraceptive exposure information probably lessened misclassification of contraceptive exposure (*9*).

TABLE 10.—*Percentage of control women ever having a breast examination by ever use of hormonal contraceptives and by selected characteristics*

Characteristic	Percent with examination			
	DMPA use[a]	No DMPA use[a]	OC use	No OC use
Age at index date, yr				
25-34	52.6	50.2	52.8	46.6
35-39	87.5	56.2	61.5	51.0
40-44	70.0	52.9	56.2	53.4
45-49	16.7	41.1	48.3	36.4
50-54	25.0	35.8	62.5	27.2
55-58	—	—	80.0	36.4
Parity[b]				
0-1	16.2	42.9	44.2	36.6
2-3	77.7	57.9	57.3	51.4
≥4	45.4	42.4	54.6	37.0
Socioeconomic status[b]				
Low	30.6	31.2	39.3	27.6
Medium	83.2	50.6	70.4	45.4
High	36.4	66.2	75.0	57.4
Region of residence[b]				
San Jose	48.0	52.8	70.5	45.4
Central Valley	69.2	52.6	60.2	46.8
Other urban areas	58.1	51.0	55.4	49.7
Other rural areas	25.8	24.7	23.0	23.3
All control women[b]	50.4	46.1	59.3	40.1

[a] Excludes control women 55-58 yr old, as none had ever used DMPA.

[b] Adjusted to age distribution of breast cancer case group (for DMPA use, cases 25-54 yr; for OC use, cases 25-58 yr).

To assess the adequacy of the exposure information among control women, we compared the prevalence rates of ever use of DMPA and OCs in February 1983 among ever-married women in the control group with the prevalence rates determined from a 1981 nationwide survey of currently married women in Costa Rica (*3*). We found almost identical prevalence rates in the two studies. No independent data source exists to assess the exposure information among the breast cancer cases. Although the controversy concerning the DMPA-breast cancer association has not received widespread attention in Costa Rica, the possibility remains that a systematic difference in recall of contraceptive use may have existed between cases and controls, which could have biased the results.

Although we have not identified any obvious bias, the elevated breast cancer risk among women who used DMPA for only a short period of time suggests that some bias that we have not been able to characterize may still account for the overall positive association. A cumulative effect of small biases associated with the following could conceivably result in a positive association such as we have found: 1) failure to interview 33% of the eligible cases, 2) possible differential detection of tumors according to DMPA use, and 3) misclassification of DMPA exposure. Moreover, the small number of DMPA users enrolled in the study increases the likelihood that chance could account for part of the elevated risk estimate.

Other studies have failed to document an association between DMPA use and breast cancer in women (*10-12*). In 1986 results were published from an ongoing, multinational, hospital-based, case-control study of steroidal contraceptives and various cancers, conducted under the auspices of the WHO (*12*). The WHO investigators reported that ever use of DMPA was associated with an RR estimate for breast cancer of 1.0 (0.7-1.5) based on 39 case users and 557 control users. No increase in risk was seen for even long-term users. Differences in study design and populations probably explain some of the discrepancies in the results between the WHO study and this one.

The results from our study in Costa Rica support the numerous scientific studies that have found that OC use does not appear to increase breast cancer risk. This is one of the first studies on this issue performed outside of North America and Europe. Results from a Los Angeles

study published in 1983 by Pike et al. (*13*) raised the possibility that use of certain "high-progestin" OC formulations before the age of 25 increases the risk of breast cancer. We found no increase in breast cancer risk associated with ever use of OCs before age 25, although we lacked a sufficient number of case users to examine the effect of duration of use before age 25. Because we did not consider use of specific OC formulations, our results do not directly address the concerns raised by Pike et al. However, as the most commonly used OC formulation in Costa Rica (50 μg ethinyl estradiol/0.5 mg norgestrel) has been one of those classified as "high progestin" by Pike et al., we believe it unlikely that an elevated risk would exist for this subgroup of OC users.

Results from another study published in 1983 (*14*) found that breast cancer risk was increased for women who had used OCs before their first full-term pregnancy. Only 2 cases and 34 controls in our study had ever used OCs before their first full-term pregnancy; the usual practice in Costa Rica is to delay contraceptive use until after 1 or more children have been born (*3*).

In summary, in this study of Costa Rican women, we found a statistically significant elevated risk of breast cancer associated with ever use of DMPA, although no dose-response effect was seen. In contrast, we found no association between OC use and breast cancer. Primarily because of the small number of DMPA users and the lack of a dose-response relationship, the results of our DMPA analysis must finally be regarded as inconclusive. Before decisions are made on whether to continue providing this effective contraceptive method, other ongoing studies will need to confirm or refute these findings.

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