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Cervical Cancer Risk and Use of Depot-Medroxyprogesterone Acetate in Costa Rica

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The relationship between cervical cancer and the use of depot-medroxyprogesterone acetate (DMPA) was examined in a nationwide case-control study in Costa Rica. Cases were women ages 25–58 years of age with invasive squamous cell cancer (N=149) or carcinoma in situ (CIS, N=415) reported by the National Tumor Registry during 1982–84. Controls (N=764) were randomly selected during a nationwide household survey. Using logistic regression, we adjusted for known risk factors for cervical cancer. DMPA use was associated with a risk of CIS of 1.1 (95% confidence interval 0.6–1.8) and a risk of invasive cancer of 1.4 (95% confidence interval 0.6–3.1). The slightly elevated risks observed may be the result of chance or a detection bias. One limitation of this study is that few women had used DMPA for longer than two years.

The long-term safety of the injectable contraceptive, depot-medroxyprogesterone acetate (DMPA), has been the subject of intense debate, chiefly because of reports of breast and endometrial neoplasia in animal studies. Most epidemiological studies of DMPA use and cancer have been hindered by small sample size and short periods of potential latency.[1-3] A recent, large case-control study by the World Health Organization (WHO) did not identify any overall increased risk of invasive cervical cancer among DMPA users.[4,5] However, women who had used DMPA for five years or more had an elevated risk of invasive cervical cancer, compared to never users (odds ratio = 2.2, 95% confidence interval, 1.2 - 4.2). This increased risk was confined to long-term users who were under 46 years of age at diagnosis or who began using DMPA before 30 years of age. The WHO study did not include cases of carcinoma *in situ* (CIS).

Costa Rica offers an opportunity to examine the relationship between DMPA use and cervical cancer, because of its high incidence of cervical cancer and the popularity of DMPA after its introduction in the early 1970s. In 1983, cervical cancer was the most commonly reported cancer and the second leading cause of cancer mortality among Costa Rican women.[6] The reported incidence of invasive cervical cancer in 1983 was 36.2/100 000 women, one of the highest rates in the world.[6] DMPA has been a popular contraceptive in Costa Rica; approximately 11% of currently married women, 15-49 years of age have used an injectable contraceptive, chiefly DMPA.[7] However, since 1983, DMPA has not been approved for contraceptive use in Costa Rica.

To further address the long-term safety of DMPA, the Costa Rican Demographic Association conducted a population-based, case-control study of cervical and breast cancer in Costa Rica in 1984-85. We report here our analysis of the association between DMPA use and cervical cancer. The breast cancer cases are the subject of a separate report.[8]

CASES

Since 1980, the Ministry of Health's National Tumor Registry has received reports of cancer diagnosis from all major hospitals and pathologists in the country.[6,9] Cases consisted of all women with invasive cervical cancer or CIS who were reported to the National Tumor Registry and had been diagnosed between 1 January 1982, and 31 March 1984. Cases were restricted to women who were 25 – 58 years of age at the time of diagnosis — the age groups likely to have used DMPA in Costa Rica. If the Tumor Registry did not have adequate information on the patient's address

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or her tumour's histological type, additional hospital records were reviewed.

CONTROLS

Controls consisted of a nationally representative, household sample of women age 25-59 years of age at the time of interview. The multistage area probability sample was based on a sampling frame from the June 1984 national census. Sample points in sparsely settled areas and near the Nicaraguan border (representing 5% of the population) were excluded, as were the cases from those areas. Although all households had an equal probability of being selected, certain age groups were over-sampled so that the age distribution of the controls would match the age distribution of the combined group of all cancers in the study.[8]

INTERVIEWS

Cases and controls were interviewed in their homes between September 1984 and February 1985. Trained female interviewers administered a standard questionnaire modified from the Cancer and Steroid Hormone Study.[10] The questionnaire obtained information on reproductive and contraceptive history and other known or suspected risk factors for cervical cancer.

Interviewers attempted to enhance recall by recording important life events and intervals of contraceptive use on a life history calendar.

Of the 938 women eligible as controls, 93% were interviewed; 89% of the 583 carcinoma *in situ* (CIS) cases were interviewed (Table 1). However, only 66% of the 293 invasive cancer cases were interviewed, chiefly because 19% of these women had died before the interview period began.

SEROLOGY

At the time of interview a laboratory technician obtained a serum specimen from cervical cancer cases and controls, after informed consent was obtained. These sera were analysed blindly with respect to case control status for antibodies to three sexually transmitted diseases: *Treponema pallidum*, *Herpes simplex* type 2 (HSV-2), and *Chlamydia trachomatis*.[11-13]

EXCLUSIONS

A panel of three Costa Rican gynaecological pathologists reviewed the interviewed cases' diagnostic cervical biopsy specimens.

Cases were excluded if the initial diagnostic biopsy specimens could not be located, if a biopsy had not been performed, or if the panel could not confirm the original histological diagnosis (Table 1). The panel also excluded cases with adenocarcinoma or adenosquamous histology because of possible differences in the epidemiology of these tumours.[14] Controls were excluded if they had a history of a cervical cone biopsy or hysterectomy.

ANALYSIS

Since interviews were conducted up to three years after the date of case diagnosis, and the exposure of interest occurred before diagnosis, we adjusted many variables to an index date. For each case, the index date was her date of diagnosis. For controls, we assigned an index date of 15 February 1983, the midpoint of the period of case eligibility. Information on the questionnaire and calendar allowed us to adjust variables related to contraceptive use and reproductive histories to the index date. Women who were not 25-58 years of age at this index date were excluded (Table 1). After all exclusions, the remaining study population consisted of 764 controls, 415 CIS cases, and 149 invasive cases. Serological specimens were available for 88.1% of the controls, 95.2% of the CIS cases, and 92% of the invasive cases.

We used logistic regression models[15] containing ever use' of DMPA and age at index date to screen for confounding effects by the following variables: socioeconomic status, education, geographical region,

TABLE 1 *Status of eligible cervical cancer cases and controls at interview and analysis*

	CIS cases	Invasive cases	Controls
Interview status	%	%	%
Eligible women	(n=583)	(n=293)	(n=938)
Completed interview	89.2	66.9	92.8
Address unknown	8.9	11.2	—
Deceased	0.2	19.1	—
Absent	0.7	0.7	3.4
Refused	0.2	0.7	2.2
Other	0.8	1.4	1.6
Total	100.0	100.0	100.0
Analysis Status			
Completed interview	(n=520)	(n=196)	(n=870)
Included in analysis	79.8	76.0	87.8
Excluded:			
Biopsy not confirmed	13.7	18.9	—
Non-squamous type	0.8	4.6	—
Prior hysterectomy	—	—	6.7
Prior cone biopsy	—	—	0.7
Age at index date			
<25 or >58	4.4	0.5	4.6
Other	1.3	0.0	0.2
Total	100.0	100.0	100.0
Women in analysis	(n=415)	(n=149)	(n=764)

marital status, gravidity, use of Papanicolaou smears, number of partners, number of spouses' previous marriages or consensual unions, age at first sexual intercourse, history of sexually transmitted disease or pelvic inflammatory disease, use of douching, tobacco use, oral contraceptive use, condom use and serological evidence of past infection with HSV-2, syphilis or chlamydia. Only seven of these variables altered the risk estimate of cervical cancer and DMPA exposure minimally, and these seven were included in the final logistic regression analysis: age (continuous), gravidity (continuous), age at first sexual intercourse (continuous), history of sexually transmitted disease or pelvic inflammatory disease (ever, never), history of a Papanicolaou smear before 1982 (ever, never), history of oral contraceptive use (ever, never), and number of sex partners (1, ≥2). Women who had never had sexual intercourse (2 CIS cases and 47 controls) were excluded from the model.

We characterized the relationship between cervical cancer and DMPA use by: ever use, total duration of use, time since first use, time since last use, and age at first use. We used the model described above to screen for interaction, that is, differences in cancer risk within subgroups of the following variables: education, socioeconomic status, age, region, gravidity, age at first sexual intercourse, number of sexual partners, STD history, and use of Papanicolaou smears, oral contraceptives, or tobacco. Additional details on study design and definitions have been published previously.[8,16]

RESULTS

On average, the CIS cases were younger than controls, while the invasive cases were older than controls—a consequence of the age-weighted control selection procedure (Table 2). Both case groups were more likely than controls to be of low socioeconomic status, to have become sexually active at a young age, to report a history of a sexually transmitted disease or pelvic inflammatory disease, and to report having three or more partners in their lifetime.

Ever users of DMPA had a risk of CIS of 1.1 when compared with never users (95% CI = 0.6–1.8, Table 3). There was no clear pattern of CIS risk by duration or time since first or last use of DMPA. Women who first used DMPA before age 30 had a CIS risk of 0.6 (95% CI = 0.3–1.7) whereas users who began use after age 39 had a risk of 2.0 (95% CI = 0.8–5.5). Both of these risk estimates were based on small numbers of users. However, when we analysed in more detail the subgroup of women who began

TABLE 2 *Per cent distribution of cases and controls by selected characteristics*

Characteristic	CIS cases (N=415)	Invasive cases (N=149)	Controls (764)
Age at index date			
25–29	22.2	7.4	19.0
30–34	29.4	20.1	20.3
35–39	21.9	12.8	16.1
40–44	14.2	16.1	13.9
45–49	7.2	13.4	13.9
50–54	3.1	14.1	11.3
55–58	1.9	16.1	5.6
Region			
Metropolitan San José	33.3	32.2	35.0
Non-metro Central Valley	34.5	23.5	33.1
Outside Central Valley	32.2	44.3	31.9
Socioeconomic status			
Low	52.1	66.4	45.7
Medium	28.7	20.1	28.8
High	19.3	13.4	25.5
Age at first coitus			
None	0.2	0.0	5.6
<16	24.6	28.2	13.9
16–17	22.2	28.2	19.2
18–19	21.9	23.5	17.2
20–21	14.0	9.4	13.7
≥22	16.9	10.1	29.8
Unknown	0.2	0.7	0.5
Number of lifetime sexual partners			
None	0.2	0.0	5.6
1	48.7	41.6	64.7
2	24.6	26.2	16.5
3	11.8	10.7	8.0
≥4	13.7	19.5	4.5
Unknown	1.0	2.0	0.8
Number of pregnancies			
0	1.7	1.3	8.8
1	7.2	3.4	8.4
2	15.2	6.7	13.5
3	19.3	6.0	17.0
4	14.5	10.1	12.7
≥5	41.9	72.5	39.5
Unknown	0.2	0.0	0.1
Number of Pap smears before 1982			
0	9.9	40.3	25.9
1–9	61.7	45.0	60.2
≥10	27.7	12.8	13.1
Unknown	0.7	2.0	0.8
History of sexually transmitted disease (STD)			
Yes	32.3	26.8	9.2
No	64.8	72.5	90.0
Unknown	2.9	0.7	0.8
STD serology			
Reactive for syphilis	9.1	17.5	6.5
Positive for HSV-2	57.5	62.8	41.5
Positive for chlamydia	68.9	73.0	57.3

using DMPA after age 39, the increased risk was confined to women who had used DMPA during the year prior to their index date. For women who first began using DMPA after age 39 and who were using DMPA during the year prior to their index date, the risk of CIS was 4.5 (95% CI = 1.0–19.7, data not in table).

Ever users of DMPA had a risk of invasive cancer of 1.4 when compared with never users (95% CI = 0.6–3.1, Table 4). However, all estimates for invasive cancer were based on only 10 cases who reported use of DMPA. The point estimates of invasive cancer risk were slightly higher for women with less than a year of use and for women with more recent use. There was no change in risk with varying age at, or time since, first use of DMPA.

Controls who reported a history of DMPA use were more likely to have had a Papanicolaou smear before 1982 than controls who had never used DMPA (89% versus 74%, Table 5). This appeared to be true in each age, geographical, and socioeconomic subgroup, although there were few DMPA users in most strata.

TABLE 3 *Risk of carcinoma in situ in relation to DMPA use by duration, time since first use, time since last use, and age at first use*

	Number of cases/ controls	Adjusted OR*	95% Confidence intervals
Ever use†			
Never	341/606	1.0	(referent)
Ever	28/40	1.1	0.6–1.8
Duration of use‡			
<1 year	16/22	1.1	0.6–2.2
1 year	7/6	1.4	0.4–4.6
≥ 2 years	4/10	1.0	0.3–3.2
Time since first use‡			
<5 years	16/19	1.3	0.6–2.6
5–9 years	6/11	0.8	0.3–2.4
≥ 10 years	5/8	1.2	0.4–3.9
Time since last use‡			
<1 year	9/13	1.2	0.5–3.0
1–4 years	10/12	1.2	0.5–3.1
≥ 5 years	8/13	1.0	0.4–2.4
Age at first use‡			
<30 years	7/14	0.6	0.3–1.7
30–39 years	11/14	1.2	0.5–2.8
≥ 40 years	9/10	2.0	0.8–5.5

* Odds ratio adjusted for age at index date, history of sexually transmitted disease or pelvic inflammatory disease, gravidity, age at first sexual relationship, number of partners, use of oral contraceptives, and history of Papanicolaou smears before 1982.
† Excludes 46 cases and 118 controls with unknown values for DMPA use or confounding variables.
‡ 1 case and 2 controls excluded for incomplete information on dates of DMPA use, in addition to above exclusions.

DISCUSSION

Users of DMPA in Costa Rica had a slightly elevated risk of invasive cervical cancer (OR = 1.4), but the confidence interval included 1.0. The small number of cases and the lack of a biologically plausible effect of duration and time since first use suggest that this elevated risk could have been due to chance. These findings are consistent with the WHO study's risk estimate of 1.2 for invasive cancer (95% CI = 0.9–1.8). An elevated risk of invasive cancer in the WHO study was restricted to a subgroup of women who had used DMPA for five years or longer.[5] We could not examine this group in detail in our study, since only three controls and no invasive case had used DMPA for longer than five years. In addition to the limited number of long-term users, the small number of cases in most strata limited our analysis (Table 4).

Ever use of DMPA was associated with an odds ratio for CIS of 1.1 One subgroup of cases appeared to have an elevated risk—women who began use after age 39 (OR = 2.0, 95% CI = 0.8–5.5). However, chance may explain the risk estimate for this subgroup, since the confidence interval included 1.0. Detection bias might explain the elevated risk in this and other subgroups in this study because of

TABLE 4 *Risk of invasive cervical cancer in relation to DMPA use by duration, time since first use, time since last use, and age at first use*

	Number of cases/ controls	Adjusted OR*	95% Confidence intervals
Ever use†			
Never	123/606	1.0	(referent)
Ever	10/40	1.4	0.6–3.1
Duration of use‡			
<1 year	7/22	1.7	0.6–4.7
≥ 1 year	3/16	1.2	0.3–4.5
Time since first use‡			
<5 years	5/19	1.5	0.5–4.5
≥ 5 years	5/19	1.5	0.5–4.6
Time since last use‡			
<5 years	7/25	1.6	0.6–4.3
≥ 5 years	3/13	1.2	0.3–5.0
Age at first use‡			
<35 years	5/23	1.5	0.5–4.5
≥ 35 years	5/15	1.5	0.4–4.5

* Odds ratio adjusted for age at index date, history of sexually transmitted disease or pelvic inflammatory disease, gravidity, age at first sexual relationship, number of partners, use of oral contraceptives, and history of Papanicolaou smears before 1982. Referent group consists of those who had never used DMPA.
† Excludes 16 cases and 118 controls with unknown values for DMPA use or confounding variables.
‡ 2 additional controls excluded for incomplete information on dates of DMPA use, in addition to above exclusions.

differential surveillance for disease between ever users of DMPA and never users. To identify the possibility of detection bias, we compared the percentage of women reporting a history of a Pap smear among controls who had ever used DMPA and controls who have never used DMPA. Since the controls are a representative sample of Costa Rican women, their use of Pap smears before the case eligibility period began reflects the extent to which DMPA use and cervical cancer screening are associated in the general population. If DMPA users are more likely to obtain a Pap smear than are non-users, then DMPA users with CIS would be more likely to be detected than women with CIS who did not use DMPA. Consequently, DMPA users would be overrepresented among the CIS cases, resulting in spuriously elevated risk estimates. This may explain the observed slight elevations of risk estimates, especially for CIS, which is usually identified only through Pap screening. A comparable analysis for oral contraceptives from this study suggested that detection bias might explain the positive association between oral contraceptive use and CIS in Costa Rica.[16] In contrast, screening for breast cancer is not associated with DMPA use in Costa Rica.[8]

Detection bias may have contributed to the elevated risk estimate for CIS among the subgroup of users who first used DMPA after age 39, but there were too few DMPA users in this age group to adequately assess the possibility of differential surveillance by age. However, the observation that the increased risk in this subgroup was restricted to recent users is consistent with a detection bias, since recent users are likely to be recently screened for cervical pathology in conjunction with their clinic visits.

TABLE 5 *Controls reporting at least one Papanicolaou smear before 1982 by ever use of DMPA and by selected characteristics*

Characteristic	DMPA ever user % with Pap*	DMPA never user % with Pap*
All controls	89.3	74.2
Age at index date		
25–34	90.3	77.2
35–44	87.0	75.6
≥ 45	90.7	64.8
Residence		
Metro Jan José	91.8	83.2
Non-metro Central Valley	100.0	73.5
Outside Central Valley	82.1	65.0
Socioeconomic status		
Low	88.1	65.3
Medium	83.8	77.3
High	100.0	86.7
Number of women	(45)	(719)

* Adjusted to the age distribution of the general population of Costa Rica.[19]

We attempted to minimize recall bias by the use of a life history calendar as a memory aid. Since other injectable contraceptives were used rarely by private physicians over the last decade, it is possible that some women could have confused a one-month injectable contraceptive for the three-month injectable, DMPA. However, including users of any injectable contraceptive with DMPA users did not alter the risk estimates. Interviewer training and a standard questionnaire for both cases and controls should have reduced the likelihood of an interviewer bias. However, it was not possible to keep interviewers unaware of case-control status.

Ascertainment bias should have been minimal since all hospital and pathologists in the country participate in the National Tumor Registry. In one review of hospital discharges, the registry detected 98% of women hospitalized for gynaecological malignancies.[6] In addition, the validity of the diagnosis in this study was enhanced by including only cases whose histological classification had been confirmed by a panel of gynaecological pathologists. The exclusion of cases who did not have a diagnostic biopsy confirmed by the pathology panel probably did not bias the risk estimates, because, in additional analyses that included these patients, risk estimates for DMPA use in association with CIS or invasive cancer did not change appreciably.

Although we examined the possibility of confounding by most of the established risk factors for cervical cancer, we could not examine two probable risk factors. We did not interview the male sex partners of the cases and controls about their sexual histories. However, the three STD serological tests may have served as a partial surrogate for the possible effects of the partners' sexual disease history.[17] We also could not examine exposure to human papillomavirus as a potential confounder, since no type-specific serological test is available for this group of viruses.[18] Circumcision and use of diethylstilboesterol (DES) have never been common in Costa Rica, so these topics were not included in the questionnaire.

The lack of a clear association between DMPA use and cervical cancer in this case-control study and in the WHO study[5] is reassuring, since the study designs differed. The Costa Rica study had a national, population-based design whereas WHO's was a multicentre, hospital-based design. However, the elevated risk of invasive cancer suggested by the

WHO study for long-term DMPA users who began DMPA use at an early age could not be confirmed in Costa Rica because of the rarity of long-term use. Although statistical chance in the WHO study may account for the elevated risk in this subgroup, additional investigation appears warranted. Since only 14 years had elapsed between DMPA's introduction into Costa Rica and this study's eligibility period, we would not have been able to detect cancers resulting from a longer latency effect. In addition, future studies of the relationship between cervical cancer and hormonal contraceptives should investigate the possibility of detection biases that may explain observed associations.

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