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Use of DMPA and the Risk of Cervical Carcinoma In Situ

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USE OF DMPA AND THE RISK OF CERVICAL CARCINOMA IN SITU

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EXECUTIVE SUMMARY

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Cervical cancer is a leading cause of cancer morbidity and mortality among women throughout the world. Known risk factors include low social class, multiple sexual partners, history of sexually transmitted disease (STD), low frequency of Pap smears, and smoking. Use of injectable depomedoxyprogesterone (DMPA) has been implicated as a possible risk factor for cervical cancer. However, several recent case-control studies have not shown an increased risk for cervical cancer in situ (CIS) among former or current users of DMPA.

To determine whether use of DMPA is an independent risk factor for CIS among women in Jamaica, we conducted a case-control study using cases drawn from the Kingston-St. Andrew Corporate Area. To increase the comparability of cases and controls with respect to access to and use of cervical cancer screening, controls were matched to cases by Pap smear clinic and year of Pap smear. From a total of 220 women identified as CIS cases, 147 were interviewed, and 129 had complete data and were available for an unmatched analysis. From the 945 controls selected, 365 were interviewed and 337 were available for an unmatched analysis. When matched on category of Pap smear source and year, 117 cases and 302 controls were available for a matched analysis.

Crude and adjusted odds ratios were estimated using conditional logistic regression for the matched analysis and unconditional logistic regression for the unmatched analysis. Comparison of odds ratio estimates and confidence intervals from the matched and unmatched

analyses showed that inflated odds ratios and wider confidence intervals resulted from the unmatched analysis. Bivariate comparisons showed that women recruited for the study who did not have an appropriate match were considerably different from women in the matched sample with regard to source of their Pap smear and exposure to DMPA. Since the women without an appropriate match were a likely source of bias, the results from the matched analysis are presented in this report.

Among the variables considered to be potential confounders, only age at index date (date of the diagnostic Pap smear), first intercourse before age 18, and number of pregnancies were found to be confounders. After adjusting for these confounders, the odds ratio for ever use of DMPA fell from the crude estimate of 1.7 (95% CI: 1.1-2.7) to 1.1 (95% CI: 0.6-1.9) The adjusted odds ratio for women who had used DMPA 5 years or more was elevated (OR=1.9, 95% CI: 0.7-4.8), as was the odds ratio for women who had stopped using DMPA during the year preceding their index date (OR=2.8, 95% CI: 0.7-10.7), and women who initiated use of DMPA between the ages of 20 and 24 (OR=1.4, 95% CI: 0.7-3.1).

These findings are reassuring for prospective, current, and former users of DMPA who undergo regular screening for cervical cancer. No significant increase in risk for CIS was observed with ever use of DMPA, nor were significant increases in risk seen with duration, latency, or recency of use. However, the moderate increase in risk of CIS among women who used DMPA for 5 or more years warrants further consideration.

INTRODUCTION

Cervical cancer is a leading cause of cancer morbidity and mortality among women throughout the world. The worldwide incidence of cervical cancer ranks second only to breast cancer (Stanley et al. 1987). In countries where facilities for widespread screening and early treatment of pre-malignant lesions are unavailable or inadequate, a large percentage of cervical cancer cases are diagnosed at an advanced and incurable stage.

A number of risk factors have been identified for cervical cancer. The literature reporting these studies is extensive and has been the subject of several reviews (Brinton and Fraumeni 1986; Cramer 1982; Hulka 1982). Known risk factors include low social class, multiple sexual partners, early age at first sexual intercourse, multiparity, smoking, low frequency of Pap smears, history of sexually transmitted disease (STD), particularly human papillomavirus (HPV) or herpes simplex II, and sexual promiscuity of male partners. The interrelationships among these factors are complex and sexual behavior appears to be the common link among most of them.

The concern about possible carcinogenicity of steroid hormones has provided the impetus for several epidemiologic studies evaluating the effects of hormonal contraceptive use on the risk of developing gynecologic cancers. These studies have focused primarily on combined oral contraceptives (OCs), with much less research having been done on the progestin-only contraceptives (POCs). The injectable POC, depomedroxyprogesterone acetate (DMPA), is a

highly effective contraceptive, has been commercially available in some countries since the early 1970s, and is an important component of national family planning programs in many countries throughout the world (Liskin and Blackburn 1987). Recently the United States Food and Drug Administration (USFDA) approved DMPA for marketing as a contraceptive in the United States.

Results from toxicological studies of DMPA showed an increased incidence of breast nodules in beagles and increased incidence of benign breast disease and endometrial cancer in rhesus monkeys (Liskin and Quillin 1983; Liskin and Blackburn 1987; Kaunitz 1989; WHO 1992). These results raised concern about possible increased risk of gynecologic malignancies in DMPA users. However, the animal models were unsuitable for evaluating the carcinogenic potential of DMPA in humans because healthy female beagles are predisposed to developing breast nodules and these nodules are stimulated by progestins. Also, there are differences between humans and monkeys with respect to the cell types from which endometrial cancers arise.

Since the early 1970s when DMPA became commercially available in some countries, a number of epidemiologic studies have focused on the possible association between DMPA use and cervical cancer in humans (Powell and Seymour 1971; Dabancens et al. 1974; Oberle et al. 1988; Herrero et al. 1990; WHO 1992). Findings from early studies (Powell and Seymour 1971; Dabancens et al. 1974) were inconclusive due to methodological problems which include the following: (1) small sample size; (2) inclusion of only a few women who had

used DMPA for long periods of time; (3) the possible enhanced detection of cervical cancer among users of hormonal contraception; (4) recall bias; and (5) confounding by sexual behavior, use of contraception, and other established risk factors for cervical cancer. [It is important to note that sexual behavior may be a determinant of both the type of contraception a woman selects and the risk of cervical cancer.]

More recently, three case-control studies that address many of these methodologic problems have been reported (Oberle et al. 1988; Herrero et al. 1990; WHO 1992). In a population-based case-control study in Costa Rica, Oberle and colleagues (1988) estimated the risk of cervical cancer in situ (CIS) to be virtually the same among users and nonusers of DMPA (OR=1.1, 95% CI: 0.6-1.8). However, women who had started using DMPA after the age of 39 and during the year prior to diagnosis had higher odds ratios (OR=2.0) compared with younger women.

In a hospital-based case-control study conducted in Latin America by Herrero et al. (1990), women who were current or former users of injectable contraceptives (which included primarily DMPA) had a slightly lower risk of invasive cervical cancer (OR=0.8, 95% CI: 0.5-1.2). Women who used injectable contraceptives for fewer than 5 years appeared to be at moderately lower risk of invasive cervical cancer compared with women who never used injectable contraceptives (OR=0.5, 95% CI: 0.3-0.9). However, a 2.4-fold increase (95% CI: 1.0-5.7) in the risk of this cancer was estimated for women who had used injectable contraceptives for 5 or more years. The effect of prolonged use of injectable contraceptives

was greater for women reporting first use 10 or more years before interview and last use more than 5 years before interview.

In 1981, the World Health Organization undertook a multi-country, hospital-based, case-control study to examine the relationship between the use of DMPA and OCs and the risk of cervical, breast, endometrial, and hepatic cancers (WHO 1985a; 1985b; 1985c; WHO 1986; WHO 1992). After controlling for women's sexual behavior, reproductive histories, and a number of other suspected risk factors, the relative risk of invasive cervical cancer comparing women who were current or former users of DMPA was estimated at 1.1 (95% CI: 0.96-1.29) (WHO 1992). There was no trend of increasing risk of invasive cervical cancer with increasing duration of DMPA use, time since initial or more recent use of DMPA, or age at first use.

We conducted a case-control study to determine whether use of DMPA is an independent risk factor for squamous cell carcinoma in situ of the uterine cervix and invasive cervical cancer among women in Jamaica. Advantages of the study include: (1) the use of individual matching procedures to select controls, thereby assuring that the study population was composed of women screened for cervical cancer; and (2) collection of detailed information on relevant confounders such as sexual behavior, reproductive history, smoking, and exposure to STDs. In this paper we present results showing the risk of CIS associated with DMPA use. (Note: Of 137 cases of invasive cervical cancer identified, 38 cases were deceased at the time of the study, and fewer than 40 matched cases were available for analysis.)

METHODS

Study Population and Design

The study population for this case-control study was drawn from the Kingston-St. Andrew Corporate Area of Jamaica. The prevalence of DMPA use is relatively high in Jamaica; results from the 1989 Contraceptive Prevalence Survey show that 22.7% of women ages 15 to 49 years had used an injectable contraceptive at some time in their lives (McFarlane and Warren, 1990). The high prevalence of DMPA use and the existence of a population-based tumor registry in a country with a high incidence of cervical cancer offered a unique opportunity to study the effects of DMPA use on the risk of cervical cancer while taking into account the effects of confounding variables.

Cases were identified from the Jamaica Tumor Registry, a population-based registry, and were defined as women who met the following criteria: (1) had a newly diagnosed, histologically confirmed diagnosis of carcinoma of the cervix between November 1982 and December 1987; (2) were residents of the Kingston-St. Andrew Corporate Area at the time of diagnosis; and (3) were 50 years of age or younger at the time of the diagnosis.

Case status was verified through a retrospective histological review of biopsy slides and specimens used to make the original diagnosis. An experienced histopathologist in the Department of Pathology at the University of the West Indies conducted the review blind to the original diagnosis and made a validation diagnosis. Diagnoses were based on established standard histopathological criteria as described by Buckley et al. (1982). When a discrepancy

was found between the original and validation diagnoses, the slides and specimens were reviewed by a panel of three senior pathologists blind to both diagnoses. A final histological diagnosis was developed at FHI based on the assessments made by the four histopathologists who performed the validation. The outcome of this pathological review was used to define the cases to be included in the data analysis.

For each case, three controls were randomly selected from the pool of eligible women at the same medical facility where the case obtained her diagnostic Pap smear. The medical facility where most cases obtained their Pap smears was the Jamaica Cancer Society. Other sources of Pap smears included hospital-based clinics and private physician clinics. The date the case obtained the Pap smear that led to her diagnosis is defined as the "index date" for cases. To be a control, a woman had to meet the same residency and age criteria as a case. She had to have a Class I (normal) Pap smear within 3 months of the date on which the index case had her diagnostic Pap smear. The date of the normal Pap smear that made the control eligible for the study is the "index date" for controls. A woman was excluded from the control group if she had a history of cervical cancer or a hysterectomy in which the cervix was removed before the Pap smear that made her eligible for the study.

Consent to contact the potential study participants was obtained from the attending physician of identified cases and controls. Once physician consent was granted, cases and controls were recruited by mail using letters of invitation signed by their physicians. After two mailings, home visits were made by study staff to follow up nonrespondents.

Nurses trained to administer the study questionnaire interviewed respondents at the Jamaica Cancer Society or the respondent's home. They used a structured questionnaire to obtain information on socio-demographic characteristics, reproductive history, sexual history, history of contraceptive use by specific method, use of noncontraceptive hormones, cervical cancer screening history, STD history, smoking history, and male partners. Completion of the interview took approximately 1 hour.

Study Losses and Exclusions

From a total of 373 cases and 945 controls identified, 209 cases and 365 controls were interviewed (see Table 1). Primary reasons for nonresponse prior to interview were: subject did not answer mailed request; subject not available when unanswered mailed requests were followed up with home visits; subject moved with no forwarding address; and migration out of the area. Of the 209 cases interviewed, 147 were identified in the Jamaica Tumor Registry as cases of cervical carcinoma in situ, 55 were identified as cases of invasive carcinoma and 7 had cervical neoplasia of unknown stage or histological type. A retrospective histologic review of biopsy slides and specimens used to make the original diagnosis verified 139 cases of carcinoma in situ and 45 cases of microinvasive or invasive carcinoma.

Additional women were excluded if they had a previous diagnosis of cervical cancer before the index date, a hysterectomy or cervical procedure (except diagnostic procedures such as colposcopy or biopsy) before the index date, had never been screened for cervical cancer, or had missing information on the source of the Pap smear or on DMPA exposure. After these

exclusions, there remained 129 cases of carcinoma in situ and 337 controls.

Restriction of the multivariate analysis to individually matched case-control sets resulted in the loss of a substantial number of cases and controls. Since the individually matched case-control sets were not unique with respect to the source and date of the diagnostic Pap smear, a category-matching approach was used whereby cases and controls were grouped as sets who obtained Pap smears from the same medical facility during the same calendar year. To be included in the analysis population, a case had to have at least one control in the same Pap smear clinic and Pap year stratum. Similarly, controls had to have at least one case with the same Pap smear clinic and Pap year stratum. After all exclusions and losses due to incomplete matching, the population for the category-matched multivariate analysis consisted of 117 cases and 302 controls.

Statistical Analysis

The objective of the data analysis was to compare the odds of DMPA exposure among CIS cases and their controls. The following parameters of DMPA use were considered: ever use of DMPA ; duration of DMPA use; time since last DMPA use (recency); time since first DMPA use (latency); and age at first DMPA use. The relevant period of exposure for DMPA use was defined as an exposure occurring before the index date (the date of the diagnostic Pap smear for cases; the date of the corresponding normal Pap smear for controls).

Stratified analysis techniques were used to perform exploratory analyses and to identify

potential confounders. Results from stratified analyses are presented in Tables 2 and 3. For matched analyses, the SAS procedure PHREG was used to obtain conditional maximum likelihood estimates of crude and adjusted odds ratios along with their corresponding 95% test-based confidence intervals (SAS 1991; Breslow and Day 1980). Results from multivariate analyses are presented in Tables 4 through 6. For corresponding unmatched analyses, unconditional logistic regression techniques were used in which matching variables were treated as covariates. The SAS procedure LOGISTIC was used to obtain unconditional maximum likelihood estimates of odds ratios (SAS 1991). Results for the matched and unmatched approaches were compared according to the method described for evaluating poolability by Breslow and Day (1980).

Empirical trend analysis was performed using the SAS macro EMPTREND to assess departures from linearity for all continuous and categorical variables (Harrell and Lee, 1985). Restricted cubic splines were used to assess departure from linearity for continuous covariates and to generate spline terms to model the nonlinear segments of the curves that depict the relationship between the risk factor and case-control status (Harrell et al., 1988). The SAS macro RDSPLINE was used to estimate the restricted cubic splines for continuous variables. The relationships between case-control status and women's age at index date and number of pregnancies were nonlinear, and spline terms were used for these confounders in the conditional multivariate analyses.

The process used to build the regression model to evaluate the association between DMPA

and CIS involved the following steps: an initial screen for potential confounders; construction of first order interactions between confounders and ever use of DMPA; assessment of collinearities; and assessment of interactions and evaluation of joint confounding by backward elimination (Kleinbaum et al., 1982). Potentially confounding variables were screened by comparing the odds ratio for ever use of DMPA estimated by a regression model that included age at index date, source of Pap smear, year of Pap smear, ever use of DMPA, and the potential confounder with the odds ratio estimated by an alternate model that excluded the potential confounder.

The following variables were screened as potential confounders: less than a secondary education; age at first coitus (continuous); age at first coitus (<15, 15-16, 17-19, 20+); first coitus before age 18; history of STDs; lifetime number of sexual partners (continuous); number of pregnancies (continuous); age at first Pap smear (continuous); interval between first coitus and first Pap smear (continuous); ever use of oral contraceptives; ever use of condoms; ever use of spermicides; current or past smoking; ever having a partner who smoked. (Note: the various categorization schemes for age at first coitus were tested separately.) Of these variables, only age at index date, first coitus before age 18, and number of pregnancies changed the odds ratio by more than 10%. Collinearities among ever use of DMPA, confounders and interaction terms were evaluated by a combination of simple correlation analysis and regression analysis.

Reduced models were compared with the full model (which adjusted for age at index date,

first coitus before age 18, and number of pregnancies) by systematically dropping single and paired combinations of these three confounders from the model (see Table 5). While a reduced model with number of pregnancies as the confounder was the most parsimonious model with virtually no change in the odds ratio, this reduced model did not noticeably improve the precision of the estimate. Based on the outcome of these comparisons and the inclusion of these known confounders in earlier studies of DMPA and cervical cancer, results from the full model are presented in this report.

Once the full and reduced models were determined, in order to test the need to retain matching, corresponding analyses were conducted on the category-matched population and on the 129 cases and 337 controls available for an unmatched analysis. Results from comparisons of matched versus unmatched logistic regression models for full and reduced models for ever use of DMPA are presented in Table 5. Results for comparisons of matched and unmatched analyses for the various dimensions of DMPA use are presented in Table 6. We expected that inclusion of the 47 women who were excluded due to lack of a suitable match would increase the precision of our estimates without notably changing the odds ratio estimates. Contrary to our expectation, the odds ratios from the unmatched analysis tended to be higher than those in the matched analysis and the confidence intervals were wider.

Of the 47 women added to the unmatched analysis, 31 of the 35 controls were unexposed, constituting a DMPA ever use prevalence of 11%. This rate is very low when compared with an ever use rate of 33.4% among matched controls (see Table 2). The 33.4% rate for

matched controls is more representative of the base population, given that in a screened population one would expect the rate of DMPA use to be at least equal to if not higher than the national prevalence of 22.7%. As a result of the high proportion of undiseased and unexposed women in the unmatched group, there is a striking difference between the crude odds ratio calculated for the matched sample (1.7) and that calculated for the 47 women in the unmatched group (15.5). Stratification of the unmatched women by source of the Pap smear indicates that all but one of these women were recruited into the study from a source other than the Jamaica Cancer Society. It appears that unexposed controls who had their Pap smears at a source other than the Jamaica Cancer Society were much less likely to have an appropriate match than other participants in the study. Since these woman are considerably different from those included in the matched analysis, and a likely source of bias, we present the results from the matched analysis (117 cases and 302 controls).

RESULTS

Characteristics of the Case and Control Subjects

Selected characteristics of case and control subjects are shown in Table 2. Compared with controls, case subjects were somewhat older than controls (36 years for cases and 32 years for controls) and were more likely to have had only a primary school education (53.0% and 33.4%, respectively).

The percentage of cases who had sexual intercourse for the first time before the age of 14 (21.6%) was nearly twice that of controls (12.0%). The median lifetime number of sexual

partners reported for cases and controls was similar, three for controls and four for cases. However, a larger percentage of cases (51.3%) than controls (37.9%) reported having four or more sexual partners during their lifetime. Slightly more than half of the cases (58.9%) reported a history of STDs, as did a comparable proportion of the controls. Trichomoniasis, pelvic inflammatory disease (PID), and gonorrhea were the infections most frequently reported. Only gonorrhea was reported somewhat more frequently among cases than controls.

A higher percentage of cases (73.1%) than controls (59.1%) had their first Pap smear after the age of 25. The median interval between reported age at sexual initiation and the age at first Pap smear was 8 years for controls and 13 years for cases. Almost all the cases (99.1%) and 88.1 percent of the controls reported ever having been pregnant. A higher percentage of cases than controls had four or more pregnancies (52.1% and 37.8% respectively).

The proportion of women who reported ever having smoked was almost twice as high among cases (20.5%) as among controls (11.3%). The proportion of women who had at least one sexual partner who smoked was 74.1% among cases and 59.6% among controls.

More controls (63.9%) than cases (57.3%) reported ever having used condoms for at least three consecutive months. In contrast, a slightly greater proportion of cases (28.2%) than controls (22.2%) reported ever having used spermicides. Diaphragm use was low among cases (6.8%) and among controls (5.0%). Among the cases, 70.1% reported ever use of OCs compared with 62% of the controls.

More cases (44.4%) than controls (33.4%) reported ever having used DMPA. Almost 1.5 times as many cases (22.0%) as controls (15.0%) had used DMPA for 5 or more years. The proportion of cases (48%) who had initiated DMPA use 10 or more years before the date of their diagnostic Pap smear was greater than the proportion of controls (35%) who had initiated DMPA use 10 or more years before their corresponding index date. More than twice as many cases (14%) as controls (6%) had used DMPA within the year preceding their index date.

Characteristics of the DMPA Exposed and Unexposed Subjects

Selected characteristics of women who had ever used DMPA and women who had never used DMPA are summarized in Table 3. While the median age for women who had ever used DMPA was similar to that of their unexposed counterparts (34 years and 33 years, respectively), the age range for DMPA users was narrower (20-48 years and 15-51 years, respectively). A smaller percentage of women who had used DMPA had continued their education beyond primary school (53.6%) compared with unexposed women (65.4%).

The percentage of DMPA users who had first intercourse before age 14 (21.7%) was twice that of nonusers (10.7%). The median age for first intercourse was 16 years for DMPA exposed women compared with 18 years for unexposed women. A higher percentage of DMPA users than nonusers had four or more sexual partners during their lifetime (53.4% and 34.9%, respectively). Prior history of an STD infection did not differ by DMPA use, nor did the age at which women had their first Pap smear. A higher percentage of DMPA users than

nonusers had four or more pregnancies (59.5% and 31.6%, respectively). While DMPA users were slightly more likely to smoke themselves, they were much less likely to have had sexual partners who smoked (35.3% of users versus 63.0% of nonusers).

More DMPA users than nonusers had used OCs (75% and 58.1%, respectively) and other noncontraceptive hormones (34% and 19.5%, respectively). Similar percentages of DMPA users and nonusers had used condoms and spermicides, whereas a somewhat higher percentage of DMPA users had used an IUD (25.5% and 16.5%, respectively).

Estimates of Crude Odds Ratios

The estimated crude odds ratio comparing DMPA users to never users are presented in Table 4. The crude odds ratio of 1.7 (95% CI: 1.1-2.7) obtained for the association between ever use of DMPA and CIS suggests that cases are more likely to have been DMPA users. The increasing magnitude of the odds ratios with increasing duration of DMPA use suggests a dose-response effect. The largest crude odds ratio (OR=2.5, 95% CI: 1.1-5.9), and the only one for a duration of use category that was statistically significant at an alpha level of 0.05, was estimated for women who had used DMPA for 5 years or more. Women who had initiated DMPA use 10 or more years before the index Pap smear that made them eligible for the study were 2.4 times more likely to be CIS cases than controls (95% CI: 1.3-4.3).

With respect to time since last DMPA use, cases appeared to be significantly more likely than controls to have last used DMPA within the year preceding their index date (OR=4.0, 95%

CI: 1.3-12.7). Women who initiated use of DMPA before age 20 appear to have the lowest risk of CIS as evidenced by an odds ratio of 1.4 (95% CI: 0.5-3.7), compared with ratios for women who initiated DMPA at ages 20-24 (OR=1.7) and after age 25 (OR=1.6).

Estimates of Risk Associated with DMPA Use

Ever Use of DMPA

Conditional likelihood estimates of the adjusted odds ratios from the matched analysis for the selected measures of DMPA exposure are shown in Table 6. After adjusting for age at index date, first coitus before age 18, and number of pregnancies, the conditional maximum likelihood estimate of the odds ratio dropped from the crude odds ration of 1.7 to 1.1 and the 95% confidence interval included unity (95% CI: 0.6-1.9).

Duration of DMPA Use

The odds ratios for women who used DMPA for less than 1 year, 1 to 4 years, and 5 or more years were 0.9 (95% CI: 0.4-1.8), 0.9 (95% CI: 0.5-1.9), and 1.9 (95% CI: 0.7-4.8) respectively. Only the odds ratio for women who had used DMPA 5 years or more was elevated, although the confidence interval for the odds ratio included unity.

Latency of DMPA Use

There was no increase in the odds ratio (OR=1.1, 95% CI: 0.6-2.3) observed in women who had initiated DMPA use 10 or more years before their index date, and, therefore, no suggestion of a latency effect. In addition, these was no evidence of a significantly increased

risk with the time since last use of DMPA. Only women who had stopped using DMPA during the year preceding their index date were at excess risk of CIS (OR=2.8, 95% CI: 0.7-10.7). This finding suggests a recency effect. There were only seven cases and six controls in this recency category.

Age at First DMPA Use

With respect to the age at which women initiated DMPA use, after adjusting for the effects of confounding variables, initiation of DMPA use before age 20 showed no increased risk for cervical cancer (OR=1.0, 95% CI: 0.3-3.6). Women who initiated DMPA use at ages 20-24 were at somewhat elevated, but not significant, risk (OR=1.4, 95% CI: 0.7-3.1), whereas women age 25 or older were at no increased risk (OR=0.9) of carcinoma in situ.

DISCUSSION AND CONCLUSIONS

Ever use of DMPA was not associated with carcinoma in situ of the uterine cervix. Among the variables considered potential confounders, only age at index date, first intercourse before age 18 and number of pregnancies were found to be confounders. After adjusting for these variables, the odds ratio decreased from 1.7 to 1.1. This adjusted odds ratio is similar to results reported from other recent studies of DMPA use and cervical cancer risk. Oberle et al. (1988) reported an odds ratio of 1.1 for ever use of DMPA and risk of CIS in Costa Rica. With respect to ever use of injectable contraceptives including DMPA and risk of invasive cervical cancer, Herrero et al. (1990) reported an odds ratio of 0.8 with injectable

contraceptive use, and WHO (1992) reported an odds ratio of 1.1 with DMPA use.

A threshold relationship was suggested by the odds ratios obtained from different levels of duration of DMPA use. Although not statistically significant, the risk of CIS was elevated among women who had used DMPA 5 or more years. This elevated risk for 5 or more years of DMPA use is consistent with findings by Herrero et al. (1990) who reported an odds ratio of 2.4 for invasive cervical cancer among women who had used injectable contraceptives including DMPA for 5 or more years. The lower bound for this estimate was unity.

The increased odds ratio (OR=2.8) for women who had stopped using DMPA during the year before the index date suggests a recency effect which could indicate detection bias. Since current users were not at additional risk, one possible explanation is that women who have had an abnormal cervical cytology in the year before their diagnosis may have been advised to discontinue DMPA. Given the long period of time required for the development of cervical cancer, it is doubtful that this result represents a late promotional effect.

One of the strong advantages of this study is that it was specifically designed to address the issue of detection bias. The study population was restricted to women who had undergone cervical cancer screening and controls were matched to cases based on the year and clinic where Pap smears were obtained. This increased the comparability of cases and controls with respect to opportunities for detection of cervical cancer. In the analysis, the age at first Pap smear and the interval between initiation of sexual intercourse and the first Pap smear were

evaluated as confounders. We were not able to evaluate the effects of frequency of Pap smears.

In designing the study, careful attention was paid to collecting information on many potential confounders of the association between DMPA and cervical cancer. Detailed sexual histories were obtained, and efforts were made to evaluate and control for the effects of active and passive smoking, and for the characteristics of the male sexual partners of the women in the study. However, the data available from the respondents regarding sexual behavior of male partners and their history of penile cancer and STDs were not very informative because there were a large number of women who gave "don't know" responses to these questions. A man may not disclose information to his partners about his past and current sexual relationships and about medical problems, particularly those involving genitalia.

The WHO collaborative study of DMPA and cervical cancer analyzed information on male sexual behavior collected directly from a subset of husbands at the site in Thailand (WHO, 1990). Risk of invasive cervical cancer was associated with several features of the male partner's behavior, including early age at first intercourse, number of sexual partners, visits to prostitutes, lack of condom use with prostitutes, and history of STDs. In the corresponding subset of women, the odds ratio for women who had ever used DMPA was estimated at 1.03 (95% CI: 0.75-1.42). This estimate was not appreciably changed by controlling for any aspect of the husband's sexual behavior. Similarly, Brinton et al. 1990 found that the husband's number of sexual partners (taken by direct report) related directly to cervical cancer

risk, but failed to affect the risks of invasive cervical cancer associated with OC use.

Infection with HPV or other sexually transmitted pathogens could not be evaluated directly in this study. Although cervical specimens were obtained from a subset of study subjects, these specimens were lost as a consequence of power outages occurring in the aftermath of Hurricane Gilbert. As a result, we have depended on reported history of STDs and sexual behavior as proxies for exposure to a sexually transmissible agent.

The nonresponse rates prior to interview were substantial (33% for CIS cases and 68% for controls). Repeated efforts to contact respondents were hindered by the high residential mobility of Kingston residents. The high nonresponse rate among controls is a potential source of bias if there were differences in exposure to DMPA among responders and nonresponders. If, for example, women who are more likely to change residence and migrate are also more likely to take risks and use DMPA, the resulting bias would be toward the null hypothesis of no association between DMPA use and CIS.

These findings are reassuring for prospective, current, and former users of DMPA who undergo regular screening for cervical cancer. No significant increase in risk for cervical carcinoma in situ was observed with ever use of DMPA, nor were significant increases in risk seen with latency or recency of use. However, the moderate increase in risk of CIS among women who used DMPA for 5 or more years warrants further consideration.

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Table 1. Sample Losses and Analysis Sample				
REASONS FOR LOSSES BY STUDY PHASE	CASES			CONTROLS
	IN SITU	INVASIVE	UNKNOWN	
Identified	220	137	16	945
Ineligible	4	2	0	3
Eligible	216	135	16	942
Lost by Phase				
Physician Consent	5	13	1	0
Respondent Consent	58	62	8	554
Interview	6	5	0	23
Total Lost	69	80	9	577
(% of Eligible Lost)	(31.9)	(59.3)	(56.3)	(61.3)
Interviewed	147	55	7	365
Cancer Not Validated	8	10	7	NA
Cases Interviewed and Cancer Validated	139	45	0	NA
Exclusions				
Diagnosis before Index Date	0	0	NA	1
Hysterectomy	3	0	NA	4
Cervical Procedure	NA	NA	NA	17
Never Had Pap Smear	1	3	NA	0
Never Had Sexual Intercourse	0	0	NA	3
Missing DMPA Data	2	0	NA	3
Missing Pap Source	4	0	NA	0
Total Exclusions	10	3	NA	28
(% of Interviewed Excluded)	(7.2)	(5.5)	NA	(7.7)
Subjects Eligible for Unmatched Analysis	129	42	0	337
Lost Due to Matching	12	NA	NA	35
Subjects Eligible for Matched CIS Analysis	117	NA	NA	302

Table 2. Percent Distribution of Selected Characteristics of Carcinoma *in situ* (CIS) Case and Control Subjects

Characteristic	Cases (N=117)		Controls (N=302)	
	N	%	N	%
Age at index date				
15-19	0	0.0	6	2.0
20-24	0	0.0	49	16.2
25-29	14	12.5	61	20.2
30-34	37	33.0	64	21.2
35-39	32	28.6	63	20.9
40-51	29	25.9	59	19.5
Unknown	5	—	0	—
Educational level				
Primary school only	62	53.0	101	33.4
> Primary school	55	47.0	201	66.6
Age at first coitus				
≤ 14	25	21.6	36	12.0
15-16	39	33.6	85	28.4
17-19	43	37.1	119	39.8
20 +	9	7.7	59	19.7
Unknown	1	—	1	—
Refused to answer	0	—	2	—
Lifetime number of sexual partners				
0-1	9	8.0	39	13.5
2-3	46	40.7	141	48.6
4-23	58	51.3	110	37.9
Unknown	1	—	4	—
Refused to answer	3	—	8	—

Table 2 (cont.) Percent Distribution of Selected Characteristics of Carcinoma *in situ* (CIS) Case and Control Subjects

Characteristic	Cases (N=117)		Controls (N=302)	
	N	%	N	%
History of STDs				
No	46	41.1	121	41.8
Yes	66	58.9	168	58.1
Unknown	5	—	13	—
Ever had gonnorhea				
No	103	89.6	273	91.3
Yes	12	10.4	26	8.7
Unknown	2	—	3	—
Age at first Pap smear				
≤ 19	13	12.5	32	11.9
20-24	15	14.4	78	29.0
25-29	29	27.9	64	23.8
30-34	22	21.2	41	15.2
35-39	12	11.5	40	14.9
40-48	13	12.5	14	5.2
Unknown	13	—	33	—
Age at first smear minus age at first coitus (years)				
-4 to 4	14	13.6	88	33.0
5-9	22	21.4	57	21.3
10-14	27	26.2	49	18.4
≥15	40	38.8	73	27.3
Unknown/missing	14	—	35	—
Number of Pregnancies				
0	1	0.9	36	11.9
1	5	4.3	55	18.2
2-3	50	42.7	97	32.1
≥4	61	52.1	114	37.8

Table 2 (cont.) Percent Distribution of Selected Characteristics of Carcinoma *in situ* (CIS) Case and Control Subjects

Characteristic	Cases (N=117)		Controls (N=302)	
	N	%	N	%
Ever smoked				
No	93	79.5	268	88.7
Yes	24	20.5	34	11.3
Any sexual partners ever smoked				
No	30	25.9	122	40.4
Yes	86	74.1	180	59.6
Unknown	1	—	0	—
Ever used oral contraceptives				
No	35	29.9	114	38.0
Yes	82	70.1	186	62.0
Unknown	0	—	2	—
Ever used other noncontraceptive hormones				
No	79	68.1	233	77.9
Yes	37	31.9	66	22.0
Unknown	1	—	3	—
Ever used condoms				
No	50	42.7	109	36.1
Yes	67	57.3	193	63.9
Ever used spermicides				
No	84	71.8	235	77.8
Yes	33	28.2	67	22.2
Ever used diaphragm				
No	109	93.2	287	95.0
Yes	8	6.8	15	5.0
Ever used IUD				
No	99	84.6	237	78.5
Yes	18	15.4	65	21.5

Table 2 (cont.) Percent Distribution of Selected Characteristics of Carcinoma *in situ* (CIS) Case and Control Subjects				
Characteristic	Cases (N=117)		Controls (N=302)	
	N	%	N	%
Ever used DMPA				
No	65	55.6	201	66.6
Yes	52	44.4	101	33.4
Duration of DMPA use (among DMPA users only)				
< 1 year	17	34.0	44	44.0
1-4 years	22	44.0	41	41.0
≥ 5 years	11	22.0	15	15.0
Unknown	2	—	1	—
Time since first DMPA use (DMPA users only)				
< 10 years	26	52.0	66	65.3
≥ 10 years	24	48.0	35	34.7
Unknown	2	—	0	—
Time since last DMPA use (DMPA users only)				
Current users	7	14.0	19	18.8
< 1 year	7	14.0	6	5.9
1-4 years	10	20.0	26	25.8
≥ 5 years	26	52.0	50	49.5
Unknown	2	—	0	—
Age at first DMPA use (DMPA users only)				
< 20 years	6	12.0	14	13.9
20-24 years	20	40.0	37	36.6
≥ 25 years	24	48.0	50	49.5
Unknown	2	—	0	—

Table 3. Percent Distribution of Selected Characteristics of DMPA Exposed and Unexposed Subjects

Characteristic	Exposed (N=153)		Unexposed (N=266)	
	N	%	N	%
Age at index date				
15-19	0	0.0	6	2.3
20-24	11	7.3	38	14.4
25-29	27	17.9	48	18.2
30-34	50	33.1	51	19.4
35-39	38	25.2	57	21.7
40-51	25	16.6	63	24.0
Unknown	2	—	3	—
Educational level				
Primary school only	71	46.4	92	34.6
> Primary school	82	53.6	174	65.4
Age at first coitus				
≤ 14	33	21.7	28	10.7
15-16	64	42.1	60	22.8
17-19	47	30.9	115	43.7
20 +	8	5.3	60	22.8
Unknown	1	—	1	—
Refused to answer	0	—	2	—
Lifetime number of sexual partners				
0-1	11	7.4	37	14.5
2-3	58	39.2	129	50.6
4-23	79	53.4	89	34.9
Unknown	2	—	3	—
Refused to answer	3	-	8	—

Table 3 (cont.) Percent Distribution of Selected Characteristics of DMPA Exposed and Unexposed Subjects

Characteristic	Exposed (N=153)		Unexposed (N=266)	
	N	%	N	%
History of STDs				
No	55	38.5	112	43.4
Yes	88	61.5	146	56.6
Unknown	10	—	8	—
Ever had gonorrhea				
No	130	87.3	246	92.8
Yes	19	12.8	19	7.2
Unknown	4	—	1	—
Age at first Pap smear				
≤ 19	19	13.9	26	11.0
20-24	29	21.2	64	27.1
25-29	35	25.6	58	24.6
30-34	31	22.6	32	13.6
35-39	17	12.4	35	14.8
40-48	6	4.4	21	8.9
Unknown	16	—	30	—
Age at first smear minus age at first coitus (years)				
-4 to 4	29	21.3	73	31.2
5-9	28	20.5	51	21.8
10-14	31	22.8	45	19.2
≥ 15	48	35.3	65	27.8
Unknown/missing	17	—	32	—
Number of Pregnancies				
0	3	1.9	34	12.8
1	9	5.9	51	19.2
2-3	50	32.7	97	36.4
≥4	91	59.5	84	31.6

Table 3 (cont.) Percent Distribution of Selected Characteristics of DMPA Exposed and Unexposed Subjects				
Characteristic	Exposed (N=153)		Unexposed (N=266)	
	N	%	N	%
Ever smoked				
No	129	84.3	232	87.2
Yes	24	15.6	34	12.8
Any sexual partners ever smoked				
No	99	64.7	98	37.0
Yes	54	35.3	167	63.0
Ever used oral contraceptives				
No	38	25.0	111	41.9
Yes	114	75.0	154	58.1
Unknown	1	—	1	—
Ever used other noncontraceptive hormones				
No	101	66.0	211	80.5
Yes	52	34.0	51	19.5
Unknown	0	—	4	—
Ever used condoms				
No	58	37.9	101	38.0
Yes	95	62.1	165	62.0
Ever used spermicides				
No	113	73.9	206	77.4
Yes	40	26.1	60	22.6
Ever used diaphragm				
No	145	94.8	251	94.8
Yes	8	5.2	15	5.2
Ever used IUD				
No	114	74.5	222	83.5
Yes	39	25.5	44	16.5

Table 4. Estimated Crude Odds Ratios for the Association of DMPA Use and of Carcinoma *in situ*

DMPA History	Cases (N=117)	Controls (N=302)	Crude Odds Ratio	95% Confidence Interval
Ever use				
No	65	201	1.0	Referent
Yes	52	101	1.7*	1.1 - 2.7
Duration of use				
< 1 year	17	44	1.2	0.7 - 2.3
1-4 years	22	41	1.8	1.0 - 3.3
≥ 5 years	11	15	2.5*	1.1 - 5.9
Unknown	2	1		
Time since first use				
< 10 years	26	66	1.4	0.8 - 2.4
≥ 10 years	24	35	2.4*	1.3 - 4.3
Unknown	5	0		
Time since last use				
Current Users	7	19	1.3	0.5 - 3.3
< 1 year	7	6	4.0*	1.3 - 12.7
1-4 years	10	26	1.2	0.6 - 2.7
≥ 5 years	26	50	1.7	1.0 - 3.0
Unknown	0	2		
Age at first use				
< 20	6	14	1.4	0.5 - 3.7
20-24	20	37	1.7	0.9 - 3.2
≥ 25	24	50	1.6	0.9 - 2.9
Unknown	2	0		

* 95% CI excludes 1.0
Note: Never users of DMPA were the referent group for each comparison

Table 5. Estimated Odds Ratios for the Association of DMPA Use and Carcinoma *in situ* Adjusted for Different Confounder Subsets

	Matched Analysis[1]		Unmatched Analysis[2]	
Adjustment Variables	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
None[2]	1.7*	1.1 - 2.7	2.1*	1.4 - 3.2
MODEL 1 (FULL) Age at index date, first coitus before age 18, number of pregnancies	1.1	0.6 - 1.9	1.5	0.9 - 2.5
MODEL 2 Age at index date, first coitus before age 18	1.3	0.8 - 2.1	1.6	1.0 - 2.6
MODEL 3 Age at index date, number of pregnancies	1.2	0.7 - 2.0	1.6	1.0 - 2.7
MODEL 4 First coitus before 18, number of pregnancies	1.0[3]	0.6 - 1.7	1.4[3]	0.9 - 2.2
MODEL 5 First coitus before age 18	1.5	0.9 - 2.3	1.8 *	1.2 - 2.8
MODEL 6 (FINAL) Number of pregnancies	1.1[3]	0.7 - 1.8	1.5[3]	0.9 - 2.4

[1]Conditional logistic regression (N=117 cases; 302 controls)
[2]Unconditional logistic regression on unmatched sample (N=129 cases; 337 controls)
[3]Change from odds ratio for full model < 10%
* 95% CI excludes 1.0

Table 6. Estimated Adjusted Odds Ratios[1] for the Association of DMPA Use and Carcinoma *in situ*

DMPA History	Crude Odds Ratio	Matched Analysis[2]		Unmatched Analysis[3]	
		Adjusted Odds Ratio[1]	95% Confidence Interval	Adjusted Odds Ratio	95% Confidence Interval
Ever use					
No	1.0	1.0	Referent	1.0	Referent
Yes	1.7	1.1	0.6 - 1.9	1.5	0.9 - 2.5
Duration of use					
< 1 year	1.3	0.9	0.4 - 1.8	1.1	0.6 - 2.1
1-4 years	1.8	0.9	0.5 - 1.9	1.4	0.8 - 2.7
≥ 5 years	2.5*	1.9	0.7 - 4.8	2.4	1.0 - 5.4
Time since first use					
< 10 years	1.3	1.0	0.5 - 1.9	1.2	0.7 - 2.1
≥ 10 years	2.2*	1.1	0.6 - 2.3	1.7	0.9 - 3.2
Time since last use					
Current Users	1.3	1.0	0.3 - 3.0	1.0	0.4 - 2.6
< 1 year	4.1	2.8	0.7 - 10.7	4.7*	1.5 - 14.8
1-4 years	1.3	1.1	0.4 - 2.8	1.3	0.6 - 3.0
≥ 5 years	1.7	0.9	0.5 - 1.7	1.2	0.7 - 2.2
Age at first use					
< 20 years	1.4	1.0	0.3 - 3.6	1.0	0.3 - 2.7
20-24 years	1.8	1.4	0.7 - 3.1	1.6	0.9 - 3.1
≥ 25 years	1.7	0.9	0.4 - 1.6	1.4	0.8 - 2.4

1 Adjusted for age at index date, first coitus before age 18, and number of pregnancies.
2 Conditional logistic regression (N=117 cases; 302 controls).
3 Unconditional logistic regression on unmatched sample (N=129 cases; 337 controls).
* 95% CI excludes 1.0
Note: Never users of DMPA were the referent group for each comparison