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Prevention and Epidemiology

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Effect of Depo-Medroxyprogesterone Acetate on Breast Cancer Risk among Women 20 to 44 Years of Age

Christopher I. Li[1], Elisabeth F. Beaber[1], Mei Tzu Chen Tang[1], Peggy L. Porter[1,2], Janet R. Daling[1], and Kathleen E. Malone[1]

Abstract

Depo-medroxyprogesterone acetate (DMPA) is an injectable contraceptive that contains the same progestin as the menopausal hormone therapy regimen found to increase breast cancer risk among postmenopausal women in the Women's Health Initiative clinical trial. However, few studies have evaluated the relationship between DMPA use and breast cancer risk. Here, we conducted a population-based case–control study among 1,028 women ages 20 to 44 years to assess the association between DMPA use and breast cancer risk. Detailed information on DMPA use and other relevant covariates was obtained through structured interviewer-administered in-person questionnaires, and unconditional logistic regression was used to evaluate associations between various aspects of DMPA use and breast cancer risk. We found that recent DMPA use for 12 months or longer was associated with a 2.2-fold [95% confidence interval (CI), 1.2–4.2] increased risk of invasive breast cancer. This risk did not vary appreciably by tumor stage, size, hormone receptor expression, or histologic subtype. Although breast cancer is rare among young women and the elevated risk of breast cancer associated with DMPA appears to dissipate after discontinuation of use, our findings emphasize the importance of identifying the potential risks associated with specific forms of contraceptives given the number of available alternatives. *Cancer Res; 72(8); 2028–35. ©2012 AACR.*

Introduction

Taken together, the results of the Women's Health Initiative (WHI) randomized controlled trials of postmenopausal hormones strongly suggest that progestational agents and medroxyprogesterone acetate (MPA), in particular, increase a woman's risk of breast cancer. Specifically, MPA in combination with conjugated estrogen was observed to increase breast cancer incidence by 24% (1), whereas users of unopposed estrogen hormone therapy (EHT) had a nonstatistically significant reduced risk (2). Thus, the progestin component of combined estrogen and progestin menopausal hormone therapy (CHT) appears to play a central role in elevating breast cancer risk.

The injectable contraceptive depo-medroxyprogesterone acetate (DMPA) is another progestin containing preparation that is widely used by women throughout the world. It contains the same progestin that was evaluated in the WHI trial. In 1992, DMPA received U.S. Food and Drug Administration (FDA) approval for use as a contraceptive, and since this time, rates of DMPA use have steadily increased in the United States (3). However, there are limited data on the relationship between DMPA and breast cancer incidence. Results across international case–control studies conducted in Costa Rica, New Zealand, Kenya, Mexico, Thailand, and South Africa are somewhat mixed, with one analysis showing that ever use of DMPA increases breast cancer risk 2.6-fold (4), one finding that it increases risk 1.2-fold (5), and two observing no association between ever use of DMPA and breast cancer risk (6, 7). However, the 3 studies evaluating recency of use consistently found that current DMPA use was associated with a 1.5- to 1.65-fold increased risk of breast cancer (5–7). Additional studies of the relationship between DMPA use and breast cancer incidence are needed because previous reports have been limited by small number of cases younger than 45 years of age, none evaluated risk according to breast cancer subtype, and the generalizability of these results to other populations such as those in more developed countries is uncertain given differences in breast cancer incidence rates, demographics, and reproductive patterns across women worldwide.

Patients and Methods

We conducted a large population-based case–control study of breast cancer among women ages 20 to 44 years living in the 3-county Seattle-Puget Sound metropolitan area (King, Pierce, and Snohomish counties) specifically designed to assess the relationship between DMPA use and breast cancer risk.

Cases were women 20 to 44 years old diagnosed with a primary invasive breast cancer between June 2004 and June 2010 with no prior history of *in situ* or invasive breast cancer.

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Potentially eligible cases residing in King, Pierce, and Snohomish counties were identified through the Cancer Surveillance System, the population-based tumor registry that serves the 13 counties of Western Washington state and participates in the Surveillance, Epidemiology, and End Results program of the National Cancer Institute (Bethesda, MD). Because controls were ascertained via random digit dialing of landline home telephone numbers, to be eligible all cases were also required to have a landline home telephone (160 potentially eligible cases without a landline telephone were identified and excluded). Of the 1,359 eligible cases identified, 1,056 (78%) were interviewed. Of those not enrolled ($n = 303$), 82% refused to be interviewed, 10% could not be located, and 8% died before an interview could be conducted. In addition to basic information on breast cancer diagnosis, we obtained information on tumor characteristics from the cancer registry and from a centralized review of pathology reports. This includes data on estrogen receptor (ER), progesterone receptor (PR), and HER2-neu (HER2) status; and tumor stage, size, and histology.

Using a combination of list-assisted (purchased randomly generated telephone numbers) and Mitofsky–Waksberg (telephone numbers randomly generated ourselves using a clustering factor of 5; ref. 8) random digit dialing methodologies, controls from the general population of female residents of King, Pierce, and Snohomish counties were identified. Controls were frequency matched within 5-year age groups to the cases. A 1:1 ratio of controls to cases was used for participants with reference dates from 2004 to 2007 and was then switched to 0.7:1 for those with reference dates from 2008 to 2010 as a result of additional funding that was obtained to increase the number of cases enrolled during the latter years of our data collection effort. A total of 90,488 random telephone numbers were pursued with multiple rounds of contacts attempted as needed. A total of 66,844 numbers were nonworking, business, cellular, paging, dedicated facsimile, or data line numbers. A total of 3,570 numbers were never answered and thus their residential status could not be determined. Earlier studies suggest that only about 20% of such numbers are indeed residential (9). Of the 20,074 residential or presumed residential numbers, 14,130 were successfully screened for eligibility. Of the remainder, 3,105 were answering machines, 2,351 reached a respondent who refused to answer the screening questions, and for 488 there were language or other communication barriers. Of the 1,489 eligible controls identified, 943 (63%) were interviewed.

For this analysis, 24 controls and 28 cases missing data on use of injectable contraceptives were excluded. Thus, our final analytic sample size consisted of 919 controls and 1,028 cases.

Data collection

The study protocol was approved by the Fred Hutchinson Cancer Research Center (Seattle, WA) Institutional Review Board, and written informed consent was obtained from all study subjects. Cases and controls were interviewed in-person and asked about their reproductive history, body size, medical history, and family history of cancer. In addition, detailed histories of all episodes of hormonal contraceptive use, including beginning and ending dates, brand, dose, route of administration, and pattern of use (number of days per month) were obtained. Our questioning was limited to exposures that occurred before each participant's reference date (month and year). The reference date used for each woman with breast cancer was her diagnosis date. As described above, controls were frequency matched to cases on reference year. The reference months assigned to controls reflected the distribution of reference months among the cases.

Statistical analysis

The primary referent category consisted of women who never used any type of injectable hormonal contraceptive. We also conducted sensitivity analyses considering alternative reference categories. These included defining women who never used any type of hormonal contraceptive as the reference category and conducting analyses limited to ever-users of hormonal contraceptives where the reference category consisted of ever-users of a noninjectable hormonal contraceptive. Because even a single DMPA shot has been shown to result in MPA measurable in serum for as long as 7.5 to 9 months after injection, ever-users of DMPA were defined as women who ever received even a single DMPA shot (10, 11). Given these pharmacokinetics, recent DMPA use was defined as having received one or more DMPA shots within 5 years of reference date similar to how recency of hormone use has been defined by the Collaborative Group on Hormonal Factors (12). Duration of use was calculated by attributing 3 months of "use" (exposure) for each DMPA shot a woman received, as the recommended prescribed regimen is shots that are administered every 3 months. Analyses focus primarily on recent DMPA use for at least 12 months because in pooled data from 54 epidemiologic studies conducted worldwide the positive relationship between oral contraceptive (OC) use and breast cancer risk was only observed among recent users for at least 12-month duration (13).

We used unconditional logistic regression to calculate ORs and their associated 95% confidence intervals (CI) to compare breast cases with controls (14). All analyses were conducted using Stata/SE version 11.2 (StataCorp LP). All models were adjusted for age (5-year categories) and reference year (continuous) as controls were matched to cases on these factors and additionally adjusted for first-degree family history of breast cancer (no/yes/missing), body mass index 1 year before reference date [$<$25.0/25.0–29.9/$\geq$30.0 kg/m^2/missing (based on WHO categories)], number of full-term pregnancies (0/1–3/$\geq$3/missing), duration of OC use (never/$<$5/5–9.9/$\geq$10 years/missing), and screening mammography (ever/never). These latter 5 covariates were selected *a priori* as potential confounders. Other variables evaluated as potential confounders included education, income, race/ethnicity (based on self-report), and age at first live birth. None of these potential confounders changed our risk estimates by more than 10% and there was no statistically significant change ($P < 0.05$) in the fit of the model with the addition of any of these potential confounders. Thus, none were added to our final statistical models.

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Table 1. Distribution of selected characteristics among controls and cases

Characteristic	Controls (N = 919) *n* (%)	Cases (N = 1,028) *n* (%)
Age, y		
20–29	24 (2.7)	23 (2.3)
30–34	81 (8.8)	84 (8.2)
35–39	261 (28.4)	287 (27.9)
40–44	553 (60.2)	634 (61.7)
Reference year		
2004–2005	302 (32.8)	295 (28.7)
2006–2007	350 (38.1)	357 (34.7)
2008–2010	267 (29.1)	376 (36.6)
Race/ethnicity		
Non-Hispanic white	752 (82.2)	804 (79.2)
African-American	31 (3.4)	51 (5.0)
Asian/Pacific Islander	82 (9.0)	115 (11.3)
Native American	19 (2.1)	26 (2.6)
Hispanic white	31 (3.4)	19 (1.9)
Missing	4	13
Education		
High school or less	88 (9.6)	121 (11.9)
Post–high school/some college	300 (32.8)	338 (33.1)
College graduate	347 (37.9)	372 (36.4)
Post-college	181 (19.8)	190 (18.6)
Missing	3	7
Annual household income		
<$25,000	72 (7.9)	79 (7.8)
$25,000–49,999	120 (13.2)	154 (15.3)
$50,000–89,999	335 (36.8)	325 (32.3)
$90,000+	383 (42.1)	449 (44.6)
Missing	9	21
First-degree family history of breast cancer		
No	794 (89.6)	800 (80.3)
Yes	92 (10.4)	196 (19.7)
Missing	33	32
BMI 1 y before reference date, kg/m^2		
<25.0	522 (57.2)	617 (60.7)
25.0–29.9	229 (25.1)	230 (22.6)
>30	162 (17.7)	170 (16.7)
Missing	6	11
Duration of OC use, y		
Never	101 (11.0)	118 (11.6)
<5.0	332 (36.2)	358 (35.1)
5.0–9.9	213 (23.3)	212 (20.8)
>10	270 (29.5)	333 (32.6)
Missing	3	7
Number of full-term pregnancies		
Never	186 (20.2)	266 (25.9)
1–2	540 (58.8)	585 (57.0)
>3	193 (21.0)	176 (17.1)
Missing	0	1

(Continued in right-hand column of this page)

Table 1. Distribution of selected characteristics among controls and cases (Cont'd)

Characteristic	Controls (N = 919) *n* (%)	Cases (N = 1,028) *n* (%)
Age at first full-term pregnancy (among parous women), y		
<25	210 (28.6)	245 (32.2)
25–29	223 (30.4)	246 (32.4)
30–34	201 (27.4)	183 (24.1)
>35	100 (13.6)	86 (11.3)
Missing	0	1
Ever had a screening mammogram		
Never	463 (50.4)	439 (42.8)
Ever	455 (49.6)	586 (57.2)
Missing	1	3

Abbreviation: BMI, body mass index.

Results

Cases and controls had generally similar distributions with respect to age, education, and income (Table 1). Cases were somewhat more likely to be African-American and Asian and less likely to be Hispanic white compared with controls. Cases were also more likely to have a first-degree family history of breast cancer, to be somewhat leaner, to have used OCs for 10 years or longer, to be nulliparous, to have a younger age at first birth, and to have ever had a screening mammogram.

Among control women, compared with never-users of hormonal contraception, ever-users of DMPA were somewhat more likely to be younger, African-American, Native American, less educated, to not have a first-degree family history of breast cancer, and to be obese and were somewhat less likely to be Asian/Pacific Islander and nulliparous (Table 2). Compared with never-users of hormonal contraception, ever-users of hormonal contraception who never used DMPA were somewhat older, more educated, and were less likely to be Asian/Pacific Islander and nulliparous.

In our primary analysis, we compared DMPA users with all nonusers of DMPA and observed that neither ever use nor recent use of DMPA was associated with breast cancer risk using multivariate adjusted statistical models (OR, 1.2; 95% CI, 0.9–1.6 and OR, 1.5; 95% CI, 0.9–2.7, respectively; Table 3). However, recent users of DMPA for 12 months or longer had a 2.2-fold increased risk of breast cancer (95% CI, 1.2–4.2). There was also some suggestion that age at first use of DMPA influenced risk as women who first used DMPA at age $\geq$35 years had a nonstatistically significant 2.0-fold (95% CI, 0.9–4.6) increased risk of breast cancer. Timing of DMPA use in relation to either first or most recent full-term pregnancy was not related to risk.

To further evaluate the relationship between DMPA use and breast cancer risk, we considered alternative reference groups. Using a reference group of never-users of any type of hormonal contraceptive (included OCs, contraceptive patches, implants,

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Table 2. Distribution of selected characteristics among controls who never used hormonal contraception, ever used DMPA, and ever used hormonal contraception but never used DMPA

Characteristic	Never used hormonal contraception (N = 91) *n* (%)	Ever used DMPA (N = 100) *n* (%)	Ever used hormonal contraception but never used DMPA (N = 728) *n* (%)
Age, y			
20–29	7 (7.7)	5 (5.0)	12 (1.6)
30–34	9 (9.9)	17 (17.0)	55 (7.6)
35–39	22 (24.2)	39 (39.0)	200 (27.5)
40–44	53 (58.2)	39 (39.0)	461 (63.3)
Race/ethnicity			
Non-Hispanic white	54 (59.3)	76 (76.0)	622 (85.9)
Asian/Pacific Islander	26 (28.6)	7 (7.0)	49 (6.8)
Other	11 (12.1)	17 (17.0)	53 (7.4)
Education			
High school or less	10 (11.0)	17 (17.0)	61 (8.4)
Post–high school/some college	25 (27.5)	43 (43.0)	232 (32.0)
College graduate	42 (46.2)	27 (27.0)	278 (38.3)
Post-college	14 (15.4)	13 (13.0)	154 (21.2)
First-degree family history of breast cancer			
No	78 (87.6)	88 (93.6)	628 (89.3)
Yes	11 (12.4)	6 (6.4)	75 (10.7)
BMI 1 y before reference date, kg/m^2			
<25.0	54 (60.0)	49 (49.0)	419 (58.0)
25.0–29.9	23 (25.6)	26 (26.0)	180 (24.9)
>30.0	13 (14.4)	25 (25.0)	124 (17.2)
Duration of OC use, y			
Never	91 (100.0)	4 (4.0)	6 (0.8)
<5.0	0 (0.0)	42 (42.4)	290 (39.9)
5.0–9.9	0 (0.0)	28 (28.3)	185 (25.5)
>10	0 (0.0)	25 (25.3)	245 (33.7)
Number of full-term pregnancies			
Never	38 (41.8)	11 (11.0)	137 (18.8)
1–2	41 (45.1)	67 (67.0)	432 (59.3)
>3	12 (13.2)	22 (22.0)	159 (21.8)
Ever had a screening mammogram			
Never	48 (52.7)	57 (57.0)	358 (49.2)
Ever	43 (47.3)	43 (43.0)	369 (50.8)

Abbreviation: BMI, body mass index.

and hormonal intrauterine devices) throughout a woman's life, recent use of DMPA for ≥12 months was associated with a 2.8-fold (95% CI, 1.3–5.9) increased risk of breast cancer. While this risk estimate was statistically significant, it is important to note that this analysis was constrained to a small numbers of cases ($n = 105$) and controls ($n = 91$) comprising the reference group of never-users of any hormonal contraceptive. A second approach restricted the analysis to women who had ever used some type of hormonal contraceptive and used a reference group of women who had ever used a hormonal contraceptive but had never used DMPA. Using this approach, recent use of DMPA for ≥12 months was associated with a 2.1-fold (95% CI, 1.1–4.0) increased risk of breast cancer.

We also evaluated the association between recent DMPA use for ≥12 months by breast cancer subtype (Table 4). While some variation in risk was observed across tumors defined by clinical factors, hormone receptor expression, proxies of molecular subtype, or tumor histology, none of these differences were statistically significant.

Discussion

This is the first large scale U.S. study specifically designed to evaluate the relationship between DMPA use and breast cancer risk. Recent users of DMPA for ≥12 months were observed to have a 2.2-fold increased risk of breast cancer in this

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Table 3. Relationship between DMPA use and risk of invasive breast cancer

DMPA use category	Controls (N = 919) *n* (%)	Cases (N = 1,028) *n* (%)	OR[a] (95% CI)
Ever use of DMPA			
Never use	819 (89.1)	907 (88.2)	1.0 (ref.)
Ever use	100 (10.9)	121 (11.8)	1.2 (0.9–1.6)
Recency of DMPA use			
Recent use (last use <5 y ago)	24 (2.6)	36 (3.5)	1.5 (0.9–2.7)
Former use (last use ≥5 y ago)	76 (8.3)	85 (8.3)	1.1 (0.8–1.5)
Last use 5–10 y ago	42 (4.6)	34 (3.3)	0.8 (0.5–1.3)
Last use ≥10 y ago	34 (3.7)	51 (5.0)	1.4 (0.9–2.1)
Duration of DMPA use among recent users			
<12 mo	9 (1.0)	4 (0.4)	0.5 (0.1–1.6)
≥12 mo	15 (1.6)	32 (3.1)	2.2 (1.2–4.2)[b]
Age at first DMPA use, y			
<25	40 (4.4)	43 (4.2)	1.1 (0.7–1.8)
25–29	27 (2.9)	39 (3.8)	1.4 (0.8–2.3)
30–34	24 (2.6)	22 (2.1)	0.8 (0.4–1.5)
≥35	9 (1.0)	17 (1.7)	2.0 (0.9–4.6)
Timing of use in relation to first full-term pregnancy			
Never had a full-term pregnancy	11 (1.2)	21 (2.0)	1.4 (0.6–3.0)
First used DMPA before first full-term pregnancy	30 (3.3)	24 (2.3)	0.8 (0.4–1.3)
First used DMPA after first full-term pregnancy	59 (6.4)	76 (7.4)	1.4 (0.9–2.0)
Timing of use in relation to most recent full-term pregnancy			
Never had a full-term pregnancy	11 (1.2)	21 (2.0)	1.4 (0.6–3.0)
First used DMPA before most recent full-term pregnancy	60 (6.5)	57 (5.5)	1.0 (0.7–1.4)
First used DMPA after most recent full-term pregnancy	29 (3.2)	43 (4.2)	1.5 (0.9–2.5)

[a]ORs are adjusted for age, year, body mass index, duration of OC use, number of full-term pregnancies, family history of breast cancer, and history of screening mammography.
[b]$P < 0.05$.

population of women 20 to 44 years of age. The relevance of both recency and duration of use were supported by no observed increase risk among either former users of DMPA (those who last used DMPA more than 5 years ago) or among recent users of DMPA for less than 12 months. Despite being conducted in a U.S. population that is demographically and culturally quite different from the diverse populations included in the previously published studies of DMPA and breast cancer risk (which included women living in Costa Rica, New Zealand, Kenya, Mexico, Thailand, and South Africa), our results are quite similar to these prior studies which found that recent DMPA use was associated with 1.5- to 1.65-fold increased risks of breast cancer (5–7).

OCs have been shown across numerous studies to confer an increased risk of breast cancer only among recent users for at least 12 months, with a pooled analysis of the world's literature showing that among young women, current users have a 24% increased risk of breast cancer, but that this risk also dissipates once OC use ceases (13). The stronger magnitude of the association with DMPA use seen in prior studies and in our own U.S.-based study compared with that seen in relation to OCs (based on the results of our analysis restricted to users of hormonal contraceptives) may be attributable to the hormonal composition of these formulations and their different pharmacokinetics. The most common forms of OCs almost all contain both estrogen and progestin, and the dosing of these hormones can either be constant (monophasic preparations) or variable (biphasic or triphasic) over the course of a monthly cycle. They most typically also involve a 1-week hormone-free break each month in between cycles. In contrast, DMPA is a progestin-only contraceptive that involves a single injection every 3 months. With respect to its pharmacokinetics, serum concentrations of MPA are maintained at approximately 1.0 ng/mL for at least 3 months following a DMPA injection. MPA levels then decline to 0.2 ng/mL in the fifth and sixth months and become undetectable 7.5 to 9 months after injection (11). Ovulation resumes once MPA levels decrease below 0.1 ng/mL (10). So on the basis of its pharmacokinetics, even a single dose of DMPA results in a relatively lengthy and sustained exposure. There are also progestin-only OCs but they are rarely used so their relationship to breast cancer risk is not well-known.

This is the first study to evaluate associations between DMPA use and risk of different breast cancer subtypes. While we observed a substantial 3.3-fold increased risk of poor

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Table 4. Relationship between recent DMPA use for ≥12 months and risk of invasive breast cancer by clinical, molecular, and histopathologic subtype

	Never use n (%)	Recent use for ≥12 mo		*P* for difference compared with the reference case group
		n (%)	OR[a] (95% CI)	
Controls	819 (89.0)	15 (1.6)	1.0 (reference)	
AJCC stage				
I	346 (88.9)	14 (3.6)	2.7 (1.3–5.9)[b]	Reference
II, III, or IV	537 (88.3)	17 (2.8)	1.9 (0.9–3.9)	0.27
Tumor size, cm				
≤2.0	481 (88.4)	16 (2.9)	2.2 (1.1–4.5)[b]	Reference
>2.0	395 (88.6)	14 (3.1)	2.1 (0.99–4.4)	0.87
ER status				
ER^+	673 (88.3)	22 (2.9)	2.1 (1.1–4.2)[b]	Reference
ER^-	226 (87.9)	10 (3.9)	2.5 (1.1–6.4)[b]	0.63
ER/PR status				
ER^+/PR^+	611 (88.3)	20 (2.9)	2.1 (1.1–4.3)[b]	reference
ER^-/PR^-	209 (88.2)	9 (3.8)	2.4 (1.0–5.8)[b]	0.69
ER/PR/HER2 status				
ER^+	673 (88.3)	22 (2.9)	2.2 (1.1–4.3)[b]	Reference
$ER^-/PR^-/HER2^-$	154 (86.5)	9 (5.1)	3.3 (1.4–7.8)[b]	0.28
ER^-/HER2+	56 (93.3)	0 (0.0)	—(—)	—
Histology				
Ductal	791 (88.4)	26 (2.9)	2.0 (1.0–3.9)[b]	Reference
Lobular	48 (94.1)	2 (3.9)	3.2 (0.7–15.2)	0.61
Other	58 (85.3)	3 (4.4)	3.7 (1.0–13.8)[b]	0.30

Abbreviation: AJCC, American Joint Committee on Cancer.

[a]ORs are adjusted for age, year, body mass index, duration of OC use, first-degree family history of breast cancer, and history of screening mammography.

[b]$P < 0.05$.

prognosis triple-negative breast cancer associated with DMPA use, this result must be interpreted cautiously given the sample size limitations of this analysis and that the risk estimates for triple-negative and ER^+ breast cancer were not statistically different. Relevant to this finding although is the observation in the only published study of OC use and risk of different breast cancer subtypes defined by ER, PR, and HER2 status among premenopausal women that OC users for at least 1 year have a 2.5-fold (95% CI, 1.4–4.3) increased risk of triple-negative breast cancer but no increased risk of non–triple-negative breast cancer (case–case comparison, $P < 0.01$; ref. 15). In this study, the risks conferred by longer durations of OC use and fewer years since last use were also greater for triple-negative than for non–triple-negative breast cancer. The biologic mechanisms underlying the potentially stronger relationships between hormonal contraceptives and risk of triple-negative breast cancer among premenopausal women are essentially unknown, but they certainly warrant further study given the relatively poorer prognosis of this more aggressive breast cancer subtype (16–21).

Another relevant comparison is with the relationship between menopausal hormone therapy and breast cancer risk. One commonly used form of combined estrogen and progestin menopausal hormone therapy, including the form most commonly used in the United States, consists of oral conjugated estrogen in combination with MPA. This specific regimen was shown in the WHI trials to increase breast cancer risk. Studies examining use of menopausal hormones show that the risk of breast cancer returns to baseline within a few years of cessation of estrogen and progestin use (12). A primary implication of these results is the importance of exogenous progestin use and MPA use in particular, as having a promotional rather than initiatory role with respect to breast cancer risk. Although we had limited statistical power to fully assess various aspects of the timing and duration of DMPA use in relation to breast cancer risk, our results are generally consistent with other studies of exogenous progestin use in this regard and they add to the evidence that MPA use specifically confers an increased risk of breast cancer.

While few studies have evaluated the relationship between DMPA use and breast cancer risk, the evidence related to recent use is remarkably consistent. However, all of these studies are observational and therefore susceptible to different forms of bias. Given our case–control design, recall bias is a potential concern. DMPA is a unique exposure although given that is in an injection and serves as a

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contraceptive for a limited time period. Thus, difficulty in recall of this exposure in a population restricted to young adults is likely not a problem appreciably enough to bias our risk estimates. Confounding is also a potential concern given the differences in women who do and do not use DMPA as shown in Table 2. However, all analyses were adjusted for multiple *a priori* confounders and additional potential confounders were also carefully assessed. Although relatively large in its overall sample size, a limitation of this study was that only 10.9% of controls and 11.8% of cases had ever used DMPA. Consequently, our statistical power to assess more detailed aspects of patterns of DMPA use was limited. Finally, the exclusion of women without a landline telephone could potentially bias our results. However, a recent study comparing women in the Seattle-Puget Sound region with and without a landline telephone found no differences in their frequencies of ever use of either injectable contraceptives or OCs (22), suggesting that any bias resulting from this exclusion is likely to have minimal impact.

Because breast cancer is relatively rare among young women, existing clinical trial data are insufficient to evaluate this relationship and launching a new trial is not feasible. Consequently, the highest level of evidence will come from observational studies such as this one purposefully designed to address the association between DMPA use and breast cancer. With the addition of the results reported here, there are now 5 studies conducted over a diverse group of countries that have observed that recent DMPA use is associated with a 1.5- to 2.3-fold increased risk of breast cancer (4–7). Mitigating the clinical and public health impact of this risk is the fact that breast cancer is rare among premenopausal women. However, there are numerous contraceptive options and so further clarifying the benefits and risks associated with each option is important as women consider what choices might be best for them.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interests were disclosed.

Authors' Contributions

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