
Memoranda / Mémoires

Depot-medroxyprogesterone acetate (DMPA) and cancer: Memorandum from a WHO meeting^{*}

Depot-medroxyprogesterone acetate (DMPA) is a long-acting progestational contraceptive, which is administered by injection. It was developed in the mid-1960s, when it was seen as a method that would be particularly useful for women seeking reversible contraception who had difficulty taking a pill every day.

DMPA has been shown to be a highly effective contraceptive, and it has proved acceptable in a variety of settings. The drug is licensed as a contraceptive in more than 90 countries and has been widely used in a number of them, such as Thailand and New Zealand. On a worldwide basis, the licensing, acceptability, and prevalence of use have been influenced by concern that DMPA may increase the risk of cancer. Cancer of the breast has been a particular concern. This Memorandum reviews comprehensively the results of toxicological tests in animals and epidemiological studies in humans concerning the carcinogenicity of DMPA.

Toxicology

DMPA has undergone thorough toxicological evaluation in a number of animal species, and has been tested in short- and long-term toxicity studies in rodents, rabbits and monkeys. It has been examined for its effect on reproduction in mice, rats and rabbits, and for carcinogenic potential in rats, mice,

beagle dogs, and rhesus monkeys. Genotoxicity tests have been performed both *in vitro* and *in vivo*. Tests of genotoxicity and carcinogenicity are discussed below.

Genotoxicity

Medroxyprogesterone acetate (MPA) was negative in the Ames test both with and without an *in vitro* metabolic activation system.^a It was also negative in the DNA damage/alkaline elution assay using Chinese hamster lung fibroblasts and in the Micronucleus test in rats.^a In dogs (1) and hamsters (2), MPA produced chromosome aberrations in germ cells when administered *in vivo*. MPA also increased the induction of sister chromatid exchange in rabbit lymphocytes (3) and in mouse kidney fibroblasts (4).

Carcinogenicity

Carcinogenicity studies have been done in monkeys, rats, mice, and dogs.

Monkeys. In 1968–1977, a ten-year study of DMPA in rhesus monkeys was done. A total of 52 monkeys were divided into 4 groups, a control group and

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^a Upjohn Corporation, unpublished reports to U.S. Food and Drug Administration (FDA), 1979, 1981

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groups that received 1, 10, or 50 times the human contraceptive dose of DMPA (5). The low-dose group had 4 animals and the other two groups had 16. There was an increased incidence of total neoplasms in the high-dose group. Endometrial carcinomas were seen in two high-dose monkeys. Because DMPA caused uterine atrophy in the monkeys, there was debate about whether the endometrial tumours were uterine in origin or originated from the endocervix, or perhaps from endometrial plaques. This debate has still not been resolved.

Mice and rats. In a study done to support an application to the U.S. Food and Drug Administration (FDA) for new drug approval, rats and mice (50 animals/sex/group) were injected intramuscularly with DMPA monthly at doses of 0, 2, 100 or 200 mg/kg (5). The control and high-dose mice were examined histologically after 18 months and the rats after 24 months. There was some increase in the incidence of malignant lymphoma, hepatoma, and haemangioma in the high-dose mice, but these findings were not considered significant by the reviewing FDA pharmacologist. There was no increase in any tumour type in the rats.

In a more recent study, BALB/c mice were treated with 40 mg MPA injected subcutaneously every 2 months for 1 year (6). Mammary adenocarcinomas were found in 16 of 40 treated mice, compared with none in the untreated control group. MPA treatment has also been reported to increase the incidence of mammary tumours in C3H (7) and SHN (8) mice.

There are a number of published studies on the promoter effect of DMPA which show that it may inhibit (9, 10) or stimulate (11) growth of dimethylbenz[a]-anthracene-induced mammary tumours in rats. The inconsistency of the results may reflect both temporal and dosage differences in experimental design (5). Recently, DMPA was shown to increase the incidence of tumours of the uterine cervix in mice treated with methylcholanthrene and a beeswax-impregnated thread, when placed inside the canal of the uterine cervix (12). DMPA treatment decreased the latency period and increased the incidence of mammary tumours in *N*-methyl-*N*-nitrosourea-treated BALB/c mice (13). In the human breast cancer cell line MCF-7, MPA initially inhibited cell growth, but following continued treatment, the effect was lost and further exposure to the drug enhanced cell proliferation (14).

Dogs. In beagle dogs, DMPA increases the incidence of both malignant and benign mammary tumours when given at doses that are at and above the human contraceptive dose. Table 1 shows data from a study which is representative of other studies of the effects

of DMPA in beagles (15). In this study, six-month-old female beagle dogs were hysterectomized prior to the start of the study. Forty dogs served as controls and 20 per group were treated with DMPA at 1, 10, or 25 times the human contraceptive dose (3, 30, or 75 mg/kg), which was given by intramuscular injection every 3 months.

Survival in this study, as in other studies of DMPA in dogs, was poor. Although 30 of the 40 control dogs survived 7 years, survival in the treated groups was 14, 0, and 1 out of 20 dogs in each of the low-, mid-, and high-dose groups, respectively. None of the control dogs developed malignant mammary tumours during the study. In contrast, malignant mammary neoplasia (some with metastases) developed in 5 dogs in the low-dose group, in 8 dogs in the mid-dose group, and in 8 dogs in the high-dose group.

In beagle dogs, progestogens stimulate pituitary secretion of growth hormone (16), which has a marked mammotrophic effect in this species (17). Different progestogens have different potencies for stimulation of the mammary gland in beagles (18). In one study (19), induction of mammary tumours by high doses of MPA was reduced by prior hypophysectomy, suggesting that enhanced pituitary secretion of growth hormone is a mechanism for MPA-induced tumours. In humans, contraceptive doses of DMPA do not alter the secretion of growth hormone (20). Thus, carcinogenicity testing of DMPA in beagle dogs results in hormonal changes not seen in humans under conditions of normal use.

The toxicological profile of DMPA is often compared to that of the orally administered steroidal contraceptives that are in use worldwide. As noted recently (21), oral doses of 19-nortestosterone derivatives (83 to 200 times greater than the human dose) produced serum drug levels in rats that were actually lower than the drug levels in humans taking the con-

Table 1: Malignant and benign mammary tumours in beagle dogs treated with 1, 10, and 25 times the human contraceptive dose of DMPA as an intramuscular injection every three months, compared with untreated dogs

	Control group	DMPA-treated:		
		1 x dose	10 x dose	25 x dose
No. of dogs	40	20	20	20
No. alive after 7 years	30	14	0	1
No. of malignant mammary tumours	0	5	8	8
Benign mammary tumours (%)	10	85	95	85

traceptive dose. In contrast, DMPA administration resulted in drug exposure far in excess of human drug exposure. Levonorgestrel was administered orally to dogs at doses up to 25 times the human dose on a mg/kg basis; no increase in tumours was noted and the drug was subsequently approved for contraception. However, when given at much higher doses, the steroid was significantly tumorigenic despite the fact that even at this high dose the animal exposure was only 7 times higher than the exposure in humans (5).

Conclusions. Because of significant differences in bioavailability, animals injected with DMPA were exposed to far greater concentrations of the progestogen than were animals tested with orally administered 19-nortestosterone derivatives. Moreover, the beagle seems to respond uniquely to DMPA and other progestogens, with an increase in serum growth hormone which is probably responsible for the tumorigenic effect of DMPA on the mammary gland. Women taking contraceptive doses of DMPA have no significant elevation of serum growth hormone.

Considering all the available toxicological data there seems to be no reason to believe that DMPA is different from other progestogens in its tumorigenic potential.

Breast cancer

Although now considered an inappropriate model the effect of DMPA on mammary tumours in beagle dogs has made its effect on breast cancer in humans of particular concern. The lack of widespread use of DMPA has hampered the epidemiological study of breast cancer in relation to DMPA use. Only recently have high quality epidemiological data on this topic become available.

Epidemiological studies. The results of six epidemiological studies of DMPA and breast cancer have been published. Four early studies (22–25) all suffer from severe methodological problems and do not contribute to an understanding of the relationship between DMPA and breast cancer.

Table 2 summarizes the two case-control studies (26, 27) that provide meaningful information on the risk of breast cancer in users of DMPA. The first study (26) was a population-based case-control study that involved the entire country of New Zealand. The second study (27) was a WHO hospital-based case-control study in which data were gathered in five centres in three countries. Both studies enrolled a large number of cases of breast cancer, and the prevalence of use of DMPA in the control groups of both studies was greater than 10%. The estimated relative risk of breast cancer in women who have ever used DMPA was 1.0 in the New Zealand study and 1.21 in the WHO study.

In both studies, there was no trend in risk with the duration of DMPA use. The estimated relative risk of breast cancer for women of all ages who had used DMPA for 3 or more years was 0.93 (95% CI, 0.62–1.41) in the WHO study. Estimated risk was 1.2 (95% CI, 0.59–2.2) for women who used DMPA for 6 or more years in the New Zealand study.

Table 3 shows the results of analyses of data examining the risk of breast cancer in women who have ever used DMPA, by age at diagnosis and by age at first use. Both studies show evidence of an association of ever having used DMPA with increased risk of breast cancer diagnosed before 35 years of age. There was no association of DMPA use with increased risk of breast cancer diagnosed after age 35 years in either study.

Table 4 shows results of analyses from the New Zealand and WHO studies which examined breast cancer risk in relation to time since first use and time since last use. In both studies, estimates of relative risk were highest in relation to recent use. Younger women tend to be more likely to be recent users and this may explain the apparent effect of age at diagnosis.

Both the New Zealand and WHO studies considered use of DMPA relative to first full-term pregnancy. The numbers of exposed women were very small, and firm conclusions about risk could not be drawn for this reason.

Conclusions. Epidemiological studies provide reassurance that use of DMPA does not increase breast

Table 2: Summary of the New Zealand (26) and WHO (27) case-control studies (estimated relative risk (RR) and 95% confidence intervals (CI))

Description	Age range (years)	No. of subjects		Ever used DMPA among controls (%)	RR (95% CI) in ever-users
		Cases	Controls		
New Zealand: population-based	25–54	891	1864	13.5	1.0 (0.8–1.3) ^a
WHO-coordinated: hospital-based	<63	869	11 890	12.2	1.21 (0.96–1.52) ^b

^a Adjusted for age, parity, ethnic group, and year of interview

^b Adjusted for age, centre, and age at first live birth.

Table 3 Estimated relative risk (RR) with 95% confidence intervals (CI) for breast cancer in ever-users of DMPA, by age at diagnosis and by age at first use, in two studies on DMPA and breast cancer

Study and reference	By age at diagnosis		By age at first use	
	Years	RR (95% CI)	Years	RR (95% CI)
New Zealand (26)	25-34	2.0 (1.0-3.8) ^{a,b}	<25	1.5 (0.85-2.6) ^a
	35-44	0.94 (0.65-1.4)	25-29	0.79 (0.50-1.3)
	45-54	0.95 (0.63-1.4)	≥30	1.1 (0.75-1.5)
WHO-coordinated (27)	<35	1.40 (0.88-2.22) ^a	<25	1.32 (0.81-2.17) ^c
	35-44	1.08 (0.75-1.55)	≥25	1.21 (0.96-1.53)
	≥45	1.01 (0.68-1.51)		

^a Adjusted for age, parity, ethnic group and year of interview

^b Test for trend with duration of use: *P* < 0.001.

^c Adjusted for age, centre, and age at first live birth

cancer risk overall. Elevated risks in the same or similar subgroups were observed in the WHO and New Zealand studies. These patterns of elevation in risk are difficult to interpret. They would be consistent with an acceleration in detection of pre-existing cancer, but other interpretations are possible. The data are not compatible with an effect of DMPA as an initiating agent. Our limited understanding of how progestogens act on the human breast does not allow us to interpret the data further.

Recommendations. Further epidemiological studies of DMPA and breast cancer should be designed to clarify issues raised in existing studies. In particular, they should seek to distinguish between any effect of recent use and any effect of breast cancer occurring at a young age. Further studies should, however, include women in all age groups that have been exposed.

Research is needed on the biological mechanisms of action of progestogens on the human breast.

Cervical cancer

Data from epidemiological studies of cervical neoplasia in users of combined oral contraceptives suggest that such use may increase the risk of intra-epithelial and invasive cervical cancer, although concern about residual confounding makes a definitive conclusion impossible at present (28). It is uncertain whether the possible effect of combined oral contraceptives on risk of cervical neoplasia is due to the estrogenic or the progestogenic component, or to both. Therefore, questions have been raised about the possible role of DMPA, a progestogen, in cervical carcinogenesis.

Epidemiological studies. There are only two epidemiological studies that have assessed the relationship between DMPA and invasive cervical cancer (29, 30). Both of these were case-control studies and the relevant findings are summarized in Table 5. The relative risk of invasive cervical cancer was above

Table 4: Estimated relative risk (RR) with 95% confidence intervals (CI) for breast cancer in ever-users of DMPA, by time since first and last use, in two studies on DMPA and breast cancer.

Study and reference	By time since first use		By time since last use	
	Months	OR (95% CI)	Months	RR (95% CI)
New Zealand (26)	<60	1.7 (0.88-3.4) ^a	<60	1.6 (1.0-2.5) ^a
	60-119	1.2 (0.76-1.9)	60-119	0.99 (0.65-1.5)
	120-179	0.92 (0.64-1.3)	≥120	0.78 (0.53-1.2)
	≥180	0.73 (0.39-1.4)		
WHO-coordinated (27)	≤48	2.02 (1.35-3.01) ^b	Current	1.65 (1.08-2.52) ^a
	49-96	1.24 (0.81-1.90)	≤12	1.17 (0.53-2.56)
	97-156	0.90 (0.60-1.36)	13-36	1.29 (0.74-2.20)
	≥157	1.04 (0.68-1.58)	37-84	1.09 (0.68-1.75)

^a Adjusted for age, parity, ethnic group, and year of interview

^b Adjusted for age, centre, and age at first live birth

Table 5: Summary of results of two studies of DMPA and invasive cervical cancer (estimated relative risk (RR) with 95% confidence intervals (CI))

Study location and reference	Controls	Number of subjects		RR (95% CI)	
		Cases	Controls	Ever-used DMPA	Long-term DMPA use
Costa Rica (29)	Population-based	133	646	1.4 (0.6–3.1) ^a	1.2 (0.3–4.5) ^{a,b}
Thailand, Kenya, Mexico (30)	Hospital-based	2009	9583	1.1 (0.96–1.29) ^c	1.2 (0.84–1.72) ^{c,d}

^a Adjusted for major identified confounding factors.

^b Use for one or more years

^c Adjusted for age, number of pregnancies, number of prior Pap smears, use of oral contraceptives

^d Use for more than 8 years

1.0 in both studies, but the 95% confidence intervals did not exclude 1.0 in either of them. In neither the Costa Rica study (29) nor the WHO study (30) was there a consistent pattern of risk of invasive cervical cancer with the duration of use or with time since first or last use.

A third study (31) assessed the use of injectable contraceptives and the risk of invasive cervical cancer. Of the injectable users 55% used monthly injectable(s) and 45% reported use of a 3-monthly injectable (presumed to be DMPA). The overall estimate of relative risk for women who ever used injectable contraceptives was 0.8. The findings are difficult to interpret because separate analyses for different types of injectable preparations were not presented.

The relationship between DMPA and carcinoma *in situ* of the cervix was studied in Costa Rica (29) and in two small cohort studies (32, 33). In the Costa Rica study (29), there were 369 cases of carcinoma *in situ*. The relative risk in women who had ever used DMPA was estimated to be 1.1 (95% CI, 0.6–3.1) after adjustment for the main recognized risk factors for cervical neoplasia. In long-term (≥ 2 years) users, the adjusted relative risk estimate was 1.0 (95% CI, 0.3–3.2). There was no consistent pattern of risk of carcinoma *in situ* with duration of use, with time since first or last use, or with age at first use in this study. Because of the small size and other methodological limitations, the two cohort studies are not considered here.

Conclusions. Findings from studies of DMPA and invasive cervical cancer are generally reassuring. The results of the studies show no overall increase in risk of cervical cancer. In none of the studies to date was there a consistent pattern of risk with the duration of use or with other time-related factors. These findings do not support an association between DMPA and cervical cancer.

Recommendations. Additional studies of invasive cervical cancer and DMPA should be conducted. These studies should include collection of biological

specimens to allow the assessment of risk separately for women with and without evidence of human papilloma virus infection.

Endometrial cancer

Factors that increase exposure of the uterus to unopposed estrogen, endogenous or exogenous, produce a progression of endometrial changes from benign proliferation to atypical hyperplasia to adenocarcinoma (34). In post-menopausal women, the administration of a progestogen with exogenous estrogen mitigates the carcinogenic effect of estrogen on the endometrium (35). There is a highly significant trend of decreasing risk of endometrial cancer with increasing duration of use of combined oral contraceptives (36). These observations suggest, on theoretical grounds, that DMPA might decrease the risk of endometrial cancer.

Epidemiological studies. Two epidemiological studies with information on DMPA and endometrial cancer have been carried out (24, 37). The first study (24), a record linkage study of women attending a large family planning clinic in the USA, observed only one case of leiomyosarcoma among 5000 women who received at least one DMPA injection. No endometrial cancers occurred whereas the expected number was 0.83. Because of the small number of cases expected and the possibility that cancers were not ascertained completely in members of the cohort, no meaningful conclusion can be drawn from this study.

In a multicentre WHO study (37), only the centres in Thailand provided enough women who used DMPA to contribute to the analysis. There were 122 women with pathologically confirmed endometrial cancer and 939 controls. There were 3 cases and 84 controls who had ever used DMPA. The estimated relative risk of endometrial cancer in ever-users of DMPA was 0.21 (95% CI, 0.06–0.79). All 3 women with endometrial cancer who had used DMPA had also received estrogen premenopausally. The protective

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effect of DMPA for endometrial cancer appeared to be at least as strong as for use of combined oral contraceptives.

Conclusions. Taken together with other information about the effects of progestogens on the endometrium, data from the WHO study provide evidence that DMPA protects against endometrial cancer.

Recommendations. Studies should be undertaken to determine if the protective effect of DMPA, observed in Thailand (37), occurs in other populations. Studies should be done to determine whether past use of DMPA continues to exert a protective effect on endometrial cancer risk in older women, taking into account the influence of menopausal hormone therapy.

If estrogen is used with DMPA, the effect of this practice on risk of endometrial cancer should be evaluated.

Ovarian cancer

A number of lines of evidence implicate risk of ovarian cancer with ovulatory activity. In general, factors that are associated with reduced ovulation are associated with a lower risk of epithelial ovarian cancer (38). Taking oral contraceptives substantially reduces the risk of epithelial ovarian cancer. Five or more years of use is associated with a 50% reduction in risk (39). Since DMPA inhibits ovulation, it might also be expected to reduce the risk of ovarian cancer.

Epidemiological studies. Two epidemiological studies have assessed the risk of ovarian cancer in DMPA users. The first study of women attending a family planning clinic described earlier (24) observed 1 case of ovarian cancer in women who had at least one DMPA injection, whereas 1.16 cases were expected. The small number of cases of ovarian cancer and concern that cases of cancer may not have been completely ascertained limit the conclusions based on this study.

The question of DMPA and ovarian cancer was assessed in a WHO study (40). A total of 224 women with histologically confirmed epithelial ovarian cancer were compared with 1781 hospital controls matched by age, hospital, and year of interview. The estimated relative risk of ovarian cancer in women who had ever used DMPA, adjusted for the number of live births and oral contraceptive use, was 1.07 (95% CI, 0.6–1.8).

Conclusions. Data from the WHO study found that DMPA use was not associated with either an increased or decreased risk of ovarian cancer. The low power of the study to detect changes in risk in long-term DMPA users is a limitation. Given the

public health importance of ovarian cancer in many countries, more data are required in order to clarify this issue.

Recommendations. Studies are needed to determine whether the lack of association between DMPA use and epithelial ovarian cancer risk seen in Thailand is confirmed. Studies are needed to determine the biological mechanisms of epithelial ovarian carcinogenesis, with particular attention to the ovulation inhibition hypothesis.

Overall conclusions

The Group concluded that there was no evidence for an overall increase in risk of cancer in users of DMPA at any of the four sites reviewed (breast, cervix, endometrium and ovary). Given this evidence, the Group does not recommend restriction of DMPA use as a contraceptive on the grounds of risk of neoplasia.

Although an increased risk of breast cancer has been observed in certain subgroups of women using DMPA, these findings are difficult to interpret. It is unlikely that these observations represent new tumours caused by DMPA. There is good evidence for protection against endometrial cancer.

Much of the epidemiological information regarding DMPA and cancer comes from a single, well-conducted study, and conclusions drawn from epidemiological observations are more secure when based on a more extensive body of evidence. Additional research is needed to confirm or refute existing findings, as well as to address additional issues. In particular, the Group noted that more data were needed on long-term use by young women and that the effect of estrogen use in combination with DMPA should be evaluated.

In assessing the benefits and risks of DMPA it would be a failure of perspective to consider cancer in isolation. In deciding whether to choose this method of contraception, women and family-planning providers need to consider all the benefits and risks.

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