

# Progesterone-Only and Non-Hormonal Contraception in the Breast Cancer Survivor: Joint Review and Committee Opinion of the Society of Obstetricians and Gynaecologists of Canada and the Society of Gynecologic Oncologists of Canada.

This Review and Committee Opinion has been reviewed and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada and of the Society of Gynecologic Oncologists of Canada.

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## Abstract

**Objective:** To examine the relationship between progestin-only contraception and breast cancer, and to make recommendations regarding contraception for the breast cancer survivor.

**Outcome:** Incidence of breast cancer among users of progestin-only contraception.

**Key Words:** Breast cancer, contraceptives, progestins, progesterone

**Evidence:** PubMed and Medline databases were searched using the terms "breast cancer" and "progesterone," "contraception," "depot medroxyprogesterone acetate," "Micronor," "Mirena," and "subdermal implant." The citations were limited to the English language. References were searched for other relevant articles. The quality of evidence is described using the classification of the Canadian Task Force on the Periodic Health Exam.

**Benefits, Harms, and Costs:** Providing reliable contraception and non-contraceptive benefits to breast cancer survivors versus breast cancer recurrence risk.

## Summary Statements:

1. Progesterone and progestins can have a proliferative, antiproliferative, or neutral effect on breast tissue, depending on the type, timing, and dose of progestin used. (I)
2. Use of depot medroxyprogesterone acetate (DMPA) does not increase the risk of breast cancer in the general population. (II-2)
3. Although not as well-studied as the combined contraceptive pill, progestin-only pills do not appear to increase the risk of breast cancer in the general population. (II-2)
4. There is insufficient evidence to comment on risk or recurrence risk of breast cancer with contraceptive implants in the general population (II-2) or among breast cancer survivors. (III)
5. The limited data available suggest that the levonorgestrel-releasing intrauterine system (LNG-IUS) does not seem to increase breast cancer risk in the general population. (II-2)
6. Sterilization and the copper intrauterine device (IUD) are the most reliable non-hormonal contraceptive methods. (II-1)
7. Other non-hormonal methods may also be appropriate given decreased fertility with advancing age and after chemotherapy. (III)
8. Further research into progestin-only contraception in the breast cancer survivor is needed. (III)

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**Recommendations:**

1. DMPA use in a breast cancer survivor can be considered in circumstances where contraceptive or non-contraceptive benefits outweigh any unknown potential increase in recurrence risk. (III-C)
2. Use of progestin-only pills in a breast cancer survivor may be considered in a situation where known benefits outweigh any unknown potential increase in recurrence risk. (III-C)
3. Use of the LNG-IUS in the breast cancer survivor can be considered if the unique contraceptive or non-contraceptive benefits outweigh the risk of an unknown effect on recurrence. (III-C)
4. Non-hormonal contraceptive methods should be used as first-line options in the breast cancer survivor. (III-C)

**Validation:** This committee opinion was reviewed by the SOGC/GOC Joint Ad Hoc Committee on Breast Cancer.

**Sponsors:** GOC and the SOGC.

J Obstet Gynaecol Can 2006;28(7):616–626

**INTRODUCTION**

**B**reast cancer is the most commonly diagnosed malignancy in women, but is second to lung cancer in terms of cancer deaths for women. If a woman lives to be 90, she will have a 1 in 9 chance of developing breast cancer in her lifetime and a 1 in 27 chance of dying from it. In 2004, there were an estimated 21 200 new cases of breast cancer with 5200 deaths in Canadian women, with a fairly low (compared with other malignancies) death-per-case ratio of 0.25.<sup>1</sup> One percent of the Canadian female population are survivors of breast cancer diagnosed in the past 15 years.<sup>1</sup>

In Canada, the incidence of breast cancer has started to stabilize, but the age-standardized mortality rate declined by 2.7% per year between 1993 and 2000.<sup>1</sup> In 2000 (the last year for which data are available), the age-standardized mortality rate was 25 per 100 000, which is the lowest rate since 1950.<sup>1</sup> This good news for women with breast cancer and their care providers means that more women are surviving breast cancer. The majority of these cases occur in older women, but an estimated 21% of women developing breast cancer in 2004 were younger than 50, and these younger women account for proportionately fewer of the deaths (12%).<sup>1</sup> This means that there is a population of women with a history of breast cancer who may still have contraceptive needs, although a woman's fertility can also be affected by the treatment of breast cancer.

The likelihood of a woman becoming menopausal, transiently or permanently, as a result of adjuvant treatment depends mostly on her age and the type of chemotherapy used.<sup>2,3</sup> Alkylating agents such as cyclophosphamide, which is used in most chemotherapy regimens for breast cancer, are considered the most gonadotoxic.<sup>2</sup> Goodwin et al. from Toronto<sup>4</sup> found that after the common "CMF" or "CEF" regimens (comprising cyclophosphamide, methotrexate, or epirubicin, and fluorouracil), 15% of 35-year-old women were menopausal at one year, and 40% of 40-year-old and

75% of 45-year-old women had become menopausal one year after therapy. They also found that the addition of tamoxifen, or tamoxifen treatment alone, resulted in a small but statistically significant increase in a woman's risk of menopause.<sup>4</sup> With the "AC" regimen (doxorubicin and cyclophosphamide), the risk of menopause after chemotherapy is lower because of a lower cumulative dose of cyclophosphamide, with an average of 34% of women of all ages becoming menopausal versus an overall risk of 69% with CMF.<sup>5</sup>

Ovarian failure as a result of chemotherapy seems to happen sooner in women older than 40, and is less likely to be reversible.<sup>3,6</sup> Women younger than 40 account for only 4.4% of breast cancer cases in Canada (with only 0.4% occurring in women younger than 30).<sup>1</sup> By contrast, 17% of breast cancers in Canada arise in women aged 40 to 49.<sup>1</sup> So, among premenopausal women, those older than 40 are more likely to develop breast cancer, but the majority will become menopausal as a result of treatment.<sup>4</sup> The relatively few women under 40 who are survivors of breast cancer are less likely to become amenorrheic and therefore will have ongoing fertility concerns. For women who would like to conceive, treatment of breast cancer can have a profound impact, but others will want reliable pregnancy prevention.

A relationship between hormones and breast cancer has long been suspected on the basis of epidemiological evidence. The recent Women's Health Initiative (WHI) reported that healthy postmenopausal women using a continuous combined regimen of conjugated equine estrogen and medroxyprogesterone acetate (CEE/MPA) for more than five years had a small increase in the incidence of breast cancer compared with controls.<sup>7</sup> In their second, estrogen-only arm, the use of CEE alone for seven years was not associated with an increased incidence of breast cancer among hysterectomized women.<sup>8</sup> The results of these two trials cannot be compared directly because they involved two different populations with differing characteristics and risk factors. For example, the women in the estrogen-only trial were older, more obese, and had more prior use of hormone therapy and an earlier average age at menopause than the women in the combined CEE/MPA trial.<sup>9</sup> Despite this, several authors have inferred that these data, and other observational data suggesting a greater risk of breast cancer in women using combined estrogen/progestin therapy than for women using estrogen alone, are indicative of an adverse effect of progestins on breast cancer.

Similarly, two randomized controlled studies in Sweden (the "HABITS" [hormonal replacement therapy after breast cancer—is it safe?] trial<sup>10</sup> and the Stockholm trial<sup>11</sup>) looked at recurrence risk in postmenopausal survivors of

**Table 1. Criteria for quality of evidence assessment and classification of recommendations**

Level of evidence*	Classification of recommendations†
I: Evidence obtained from at least one properly designed randomized controlled trial.	A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
II-1: Evidence from well-designed controlled trials without randomization.	B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.	C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination.
II-3: Evidence from comparisons between times or places with or without the intervention. Dramatic results from uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.	D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination.
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.	E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

\*The quality of evidence reported in these guidelines has been adapted from the Evaluation of Evidence criteria described in the Canadian Task Force on the Periodic Health Exam.<sup>55</sup>

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on the Periodic Health Exam.<sup>55</sup>

early stage breast cancer treated with hormone replacement therapy versus a group given no treatment. These studies had similar methods and were therefore combined because, due to slow recruitment, neither study on its own would have adequate statistical power.<sup>11</sup> These studies, which both started in 1997, were terminated prematurely in December 2003 because the joint analysis of their combined results showed that breast cancer recurrence was significantly associated with hormone replacement therapy (hazard ratio [HR] = 1.8; 95% confidence interval [CI] = 1.03–3.10) when compared with no treatment.<sup>12</sup> However, when the results were looked at separately the HABITS trial showed a substantial increase in breast cancer recurrence (HR = 3.3; 95% CI = 1.5–7.4),<sup>10</sup> whereas the Stockholm trial did not show a statistically significant difference (HR = 0.82; 95% CI = 0.35–1.9).<sup>11</sup>

These two trials were found to be significantly heterogeneous, meaning that the difference in results is not due merely to chance. The authors of the Stockholm trial hypothesize that differences in progestin exposure may explain the discrepant results. In the HABITS trial, 46% of women took continuous combined regimens, whereas in the Stockholm trial, 50% of women took a “spacing out” regimen where MPA was taken for only two weeks every three months in an effort to minimize progestin exposure. It is theorized that the increased progestin exposure in the HABITS trial may account for the higher observed recurrence rate.<sup>11,12</sup> Caution must be used prior to generalizing these results. These studies were combined for statistical

reasons; one cannot then analyze them separately without losing statistical power. There were other differences between the study protocols and the patient population in terms of node- and hormone receptor-positive disease, and tamoxifen use.<sup>11</sup> In the Stockholm trial, there was considerable crossover between the regimens, and women in the control group were permitted to use vaginal estrogen therapy. Therefore, there may have been other factors involved in addition to differences in progestin exposure.

There are also obvious differences between hormone use in postmenopausal women and hormone use in premenopausal women for contraception. In the World Health Organization’s (WHO) eligibility criteria, progestin-only contraception is listed as category “4” in women with current or recent breast cancer (meaning it should not be used), and category “3” for women who have been disease-free for five years (meaning it should generally not be used, unless other methods are unavailable or unacceptable).<sup>13</sup>

The SOGC/GOC Joint Ad Hoc Committee on Breast Cancer decided to look at any evidence of a relationship between progestin-only contraception and breast cancer. This paper will examine data regarding depot medroxyprogesterone acetate (DMPA), the progestin-only pill, the levonorgestrel-releasing intrauterine system, and subdermal implants and their varying effects on incidence of breast cancer. Recommendations regarding contraception in the breast cancer survivor will then be discussed. Combined hormonal contraception will not be discussed here. The level of evidence and quality of recommendations

is described using the criteria and classification of the Canadian Task Force on the Periodic Health Exam (Table 1).<sup>14</sup>

### **IN-VITRO AND ANIMAL DATA**

The relationship between progestins and breast tissue is complex and often contradictory. Progestins can have a proliferative, neutral, or antiproliferative effect on breast tissue.<sup>15,16</sup> Mitotic activity within the breast is higher in the luteal phase of a normal menstrual cycle, and possibly related to high levels of progesterone.<sup>17,18</sup> Fine needle aspiration (FNA) biopsies performed in the second half of the menstrual cycle showed significantly higher breast tissue proliferation among women who were taking a combined oral contraceptive than seen in naturally cycling women, and there was a significant, positive correlation between serum progesterone or levonorgestrel levels and proliferation in breast tissue.<sup>19</sup>

In contrast, Foidart et al. looked at the effect of topical hormonal or placebo gel applied to the breasts of 40 postmenopausal women for two weeks prior to benign breast surgery in a randomized, blinded trial.<sup>16</sup> They found that progesterone combined with estradiol considerably limited the increase in epithelial proliferation that was seen with estradiol alone. The progesterone-only gel induced a low level of proliferation that was significantly higher than placebo, but much lower than estradiol alone. A similar study in premenopausal women showed that percutaneous administration of estradiol increased the number of proliferating epithelial cells, and progesterone had the opposite effect.<sup>20</sup>

The effect of a substance in tumour genesis may also depend on the timing of its administration. For example, progestins inhibited tumour development when given to rats prior to an initiating agent such as dimethylbenzanthracene, but the opposite sequence had the reverse effect.<sup>21</sup> There can also be variable effects depending on the type and dose of progestin used and the duration and pattern of treatment.<sup>22</sup>

Growth hormone (GH) and insulin-like growth factor 1 (IGF-1) are believed to promote proliferation in breast tissue. One study demonstrated that progesterone could induce secretion of these growth factors from human breast cancer explants in-vitro.<sup>23</sup> GH secretion of malignant cell lines was increased in response to progesterone even when progesterone receptors were absent. Synthetic progestins showed a variable effect on these growth factors, depending on the type of progestin used, the receptor status of the cell lines, and whether or not the cell lines were malignant.<sup>23</sup>

Animal data have also been conflicting. An increased risk of mammary tumours has been demonstrated in beagles and mice given high doses of MPA, but a similar finding was not

seen in rats or monkeys.<sup>24,25</sup> In macaque monkeys given CEE with and without MPA in doses equivalent to human postmenopausal hormone therapy, adding MPA enhanced an estrogen-induced proliferation of breast cells, but no proliferation was seen with MPA alone.<sup>26</sup> CEE in this, and other studies, has been shown to induce expression of progesterone receptors.<sup>21,26</sup> DMPA and MPA in biodegradable microspheres both inhibited the development of induced mammary tumours in rats.<sup>27</sup>

These results serve to highlight the complexities surrounding the effect of progesterone and progestins in normal and malignant breast tissue, as well as our incomplete understanding and the lack of consensus, seen by the opposing viewpoints put forward in the literature on this topic.<sup>15,16</sup>

### **SUMMARY STATEMENT**

1. Progesterone and progestins can have a proliferative, antiproliferative, or neutral effect on breast tissue, depending on the type, timing, and dose of progestin used. (I)

### **HUMAN DATA**

#### **DMPA**

More has been written about DMPA ("Depo-Provera") and risk of breast cancer than all other progestin-only contraceptive methods combined. In 1967, DMPA was introduced as a contraceptive in the current dose of 150 mg IM every 12 weeks,<sup>28</sup> and by 1978 it was in use in 70 countries.<sup>28</sup> But controversy about a possible association with breast cancer kept the American Food and Drug Administration from approving DMPA until 1992, after publication of the two largest case-control trials discussed below, and it was approved in Canada only in 1997.<sup>29</sup> The concern about a possible association with breast cancer began in the 1970s with reports that beagles treated with high doses of DMPA developed benign and malignant mammary tumours.<sup>24,25</sup> Since then, the appropriateness of the beagle as a model for breast tumorigenesis in humans has been debated, with most experts concluding that this animal is not an appropriate model because of its genetic predisposition to breast cancer.<sup>25,28,30,31</sup>

Early epidemiological studies provided contradictory results and had some methodological difficulties. No cases of breast cancer were found among a cohort of 1527 women (1270 of whom had been exposed to DMPA) who presented for breast examination in Thailand, but there was a clear sampling bias in this research.<sup>32</sup> In the early 1980s, a cohort study<sup>33</sup> and a case-control trial<sup>34</sup> looked at a population of predominantly black women from a family planning clinic in Georgia given DMPA on an investigational basis with permission from the FDA. Neither study showed an

increased risk. In the cohort study,<sup>33</sup> a group of 5003 women who received DMPA between 1967 and 1976 were followed until 1980, and the number of breast cancer cases was found to be lower than expected on the basis of the National Cancer Institute's age-specific data, even after attempting to correct for under-ascertainment due to diagnosis at other hospitals (relative risk [RR] 0.69; 95% CI 0.3–1.4). In a case-control study of the same population, Greenspan et al. found an odds ratio (OR) of 1.0, based on 30 cases and 179 controls.<sup>34</sup> This study had the advantage of prospective computerized data collection about contraceptive exposure, eliminating recall bias, but the numbers were very small, with only five exposed cases and only one who had received more than two injections of DMPA.

Lee et al. looked at exposure to DMPA and oral contraceptives among 171 women in Costa Rica with breast cancer diagnosed between 1982 and 1984, compared with 826 population-based controls. They found an OR of 2.6 (95% CI 1.4–4.7) for ever-use of DMPA among the 19 exposed cases and 49 exposed controls.<sup>35</sup> Only 10 cases had used DMPA for more than a year. They did not demonstrate a larger effect with increasing duration of continuous use; there was an increased OR in all categories of use, but women who had the longest time since first use had the highest OR (4.0), which is contrary to later findings, as outlined below. One of the main criticisms of this study was that only 67% of eligible breast cancer cases were interviewed, mostly because 20% of them had died, so the results could have been influenced by a survival or response bias. Assuming none of the deceased cases had used DMPA, the authors estimate that the OR would still have been 1.5 (95% CI not given), but they were laudably cautious about their results, calling them “inconclusive” and pointing out the need for other studies to refute or confirm their data.<sup>35</sup>

The first of the larger case-control trials was the New Zealand study by Paul et al. in 1989.<sup>36</sup> They looked at 891 women aged 25 to 54 with breast cancer diagnosed between 1983 and 1987 and compared their use of DMPA with that of 1864 community controls. The women were interviewed by telephone approximately six months after their diagnosis (or “reference date” for controls). The subjects were blinded to the study hypothesis, and the interviewers were blind to the patient's status at the start of the interview. (The history of breast cancer was usually revealed after the contraceptive history had been taken.) Corroboration was sought from general practitioners' records for some recent users, and these results agreed closely with the women's history of contraceptive use.

Based on 110 treated cases and 252 treated controls, the overall OR was 1.0 (95% CI 0.8–1.3) and there was no

increased risk with increasing duration of use.<sup>36</sup> Women with breast cancer diagnosed at younger than 35 years of age were more likely to have used DMPA than controls (OR 2.0; 95% CI 1.0–3.8). There was no increased risk of breast cancer in women who started DMPA after age 25, but there was a non-significant trend of increased risk for women who used DMPA at a younger age (OR 1.5; 95% CI 0.85–2.6). This became significant in women who had used DMPA for six years or more starting before they were 25 years old (OR 4.2; 95% CI 1.1–16.2), but the CI is quite wide since this was based on only four treated cases and six treated controls. There was a slight increase in risk for women who had used DMPA recently; the OR for use in the last five years was 1.6 (95% CI 1.0–2.5).<sup>36</sup>

The 1991 WHO study involved 869 women with breast cancer compared with 11 890 hospital-based controls in Kenya, Mexico, and Thailand.<sup>31</sup> Overall, they did not find a significant relationship between DMPA use and breast cancer (adjusted OR 1.2; 95% CI 0.96–1.52). The risk did not increase with duration of use, and was not increased in women who had initiated use of DMPA more than four years previously. There was a small increase in risk for women who had started DMPA within the past four years (overall OR 2.02; 95% CI 1.35–3.01), particularly for those younger than 35 years of age (OR 2.19; 95% CI 1.23–3.89). Current users had an elevated OR of 1.65 overall (95% CI 1.08–2.52), especially if they had started in the last four years (OR 2.58; 95% CI 1.48–4.49). This study did not find a significant elevation of risk for use before 25 years of age.

When discussing possible sources of bias, the authors considered detection bias: whether DMPA users underwent increased surveillance for breast cancer, which resulted in increased detection. However, when they analyzed the size and stage of the tumours at diagnosis, there was no indication that DMPA users had smaller, less advanced tumours, as would be the case if the tumours were discovered earlier by increased surveillance. Also, none of the countries had an organized screening program, and it was not yet routine to examine a woman's breasts or to teach breast self-examination at these family planning centres.<sup>31</sup>

The results of these two similar trials were pooled for a total of 1768 cases and 13 905 controls.<sup>30</sup> The combined analysis found no overall increase in breast cancer risk with DMPA use (OR 1.1; 95% CI 0.97–1.4), and there was no increased risk with increasing duration of use. Women younger than 35 at diagnosis had an odds ratio of 1.5 for ever-use of DMPA (95% CI 1.0–2.2), with the inexplicable finding that the highest risk occurred in those receiving only a single DMPA injection. There was no trend towards increasing risk with increasing duration of use in this age group either. There was a significantly increased risk with more than two

years of use before age 25 when women of all ages were combined (OR 4.1 for 25–36 months of use before age 25 and OR 2.9 for more than 36 months), based on five and six treated cases, respectively.

Recent or current use did increase the risk of breast cancer, with an odds ratio of 2.0 (95% CI 1.5–2.8) for use beginning in the past five years.<sup>30</sup> Only current users who were younger than 35 years had an elevated risk (OR 2.1; 95% CI 1.1–3.8). No increase in breast cancer risk was observed in women who had used DMPA more than five years previously, regardless of their duration of use. In fact, women who had used DMPA for two years or more, longer than five years ago, actually had a decreased risk of breast cancer (OR 0.60; 95% CI 0.37–0.98).<sup>30</sup>

In the pooled analysis, recent use emerged as a key risk factor.<sup>30</sup> It appeared that young age was not necessarily a risk factor in itself as much as it was a surrogate marker for recent use. The theory that DMPA or any progestin could increase proliferation in a tumour that is already present is plausible and compatible with these results, which show increased risk with recent use, but no increased risk overall. Among recent users, the observation that an increase in risk is seen with one injection does not make biological sense. The fact that there was no increased risk with more exposure goes against an effect on tumour promotion; if the latter were true, cumulative exposure should have increased the risk.

A recent multicentre case-control study from the United States compared 4575 randomly sampled women aged 35 to 64 with breast cancer diagnosed between 1994 and 1998 with 4682 random, matched controls from the same city.<sup>37</sup> Although the total number of subjects is higher than the above studies, because they excluded younger women, the number of women exposed to DMPA is comparable: 94 treated cases and 110 treated controls. This study also looked at contraceptive implants, but the numbers were small. They did not find an increased risk with having ever used DMPA (OR 0.9; 95% CI 0.7–1.2) or implants (OR 0.7; 95% CI 0.2–2.1). The risk remained insignificant when adjusted for multiple confounders, including menopausal status, and there was no difference when the results were examined in 10-year age groups. Risk was not increased in current users (in the past year), recent initiators (within 5 years), women with more than two years of use, or those who began use before age 25 or 35. Here, the authors found a reduced risk among women who had first used DMPA within the past year (OR 0.3; 95% CI 0.1–0.94), contrary to the other studies. Limitations of this study are low exposure to DMPA among subjects and limited long-term use, both explained by the fact that this medication was FDA-approved only in 1992.<sup>37</sup>

Another case-control study in a black/mixed race South African population with much higher use of DMPA showed no increased risk among 419 cases and 1625 hospital controls aged 20 to 54 years (OR 0.9; 95% CI 0.7–1.2).<sup>38</sup> Around 70% of this population had used injectable progestins, mostly DMPA, but also norethisterone enanthate, which is administered by injection every two months. The risk was not significantly elevated among long-term users or recent users in any age group. Users who had started DMPA at 18 years of age or earlier did not have an increase in risk. The only subgroup with a significantly elevated risk of breast cancer was current users aged 35 to 44 (OR 2.3; 95% CI 1.3 to 4.1). Current users younger than 35 years or aged 45 to 54 did not have a significantly elevated risk, but when these age groups were combined the overall odds ratio for current users was 1.6 (95% CI 1.1–2.3). Risks for DMPA versus norethisterone (used by 13 cases and 64 controls) did not differ.

These results are particularly reassuring because of the high usage of DMPA in this population. If DMPA truly had an adverse effect on breast cancer risk, the incidence of breast cancer should have been higher in this population where 70% have used this drug. In fact, this was not seen. The incidence of breast cancer in this study population was 23.1 per 100 000.<sup>38</sup> South African national data from 1993 to 1995 show an age-standardized incidence rate (ASIR) overall of 25.1 per 100 000 women, with a much lower incidence of breast cancer in black women (11.3 per 100 000) than in white women (70.2 per 100 000).<sup>39</sup> In Canada, for the same time period, the ASIR for breast cancer was about 99 per 100 000 women.<sup>1</sup> Clearly there are many genetic and lifestyle differences between their population and ours. The South African population has, for example, more pregnancies and longer intervals of breast feeding, both of which have been shown to dramatically reduce breast cancer incidence.<sup>40</sup> Nonetheless, the incidence of breast cancer in South Africa is comparatively quite low, despite prevalent use of DMPA.

Given the mostly reassuring results of these four largest case-control trials, it would seem that DMPA users do not have a significantly elevated risk of breast cancer in the general population. The subgroups with slightly higher risk are not consistent across the studies, which suggests the observed associations may be spurious. The absence of a dose-response relationship between DMPA and breast cancer risk would seem to argue against a causal association.

DMPA has also been reported to decrease mammographic density. In a case report,<sup>41</sup> two women were noted to have markedly increased breast density on mammography following discontinuation of long-standing DMPA use. This is of interest both because increased breast density makes

screening more difficult by increasing the number of false negative scans, and also because increased mammographic density has been linked to increased breast glandular proliferation which may reflect an increased breast cancer risk.<sup>4,15</sup> If the observation that DMPA reduces breast density is supported by further data, this could add to the reassuring information with regards to breast cancer risk and DMPA use.

### DMPA in Breast Cancer Survivors

How these data can be applied to survivors of breast cancer is difficult to say. Women with a history of cancer are already at high risk of recurrence, so one interpretation might be that any potential slight increase in risk by DMPA (if an increased risk exists at all) would seem negligible compared with such a high background risk. Women with cancer, however, are understandably unwilling to take any chance at all when it comes to their disease. On the other hand, high dose DMPA is sometimes given as adjunctive treatment for advanced or recurrent breast cancer.<sup>42</sup>

DMPA attains the highest systemic progestin concentration of all the progestin-only contraceptives. Ideally, alternative non-hormonal contraceptives should be chosen rather than DMPA for breast cancer survivors; in individual circumstances, however, the non-contraceptive effects of DMPA may afford additional benefits that outweigh potential risks.

### SUMMARY STATEMENT

2. Use of DMPA does not increase the risk of breast cancer in the general population. (II-2)

### Recommendation

1. DMPA use in a breast cancer survivor can be considered in circumstances where contraceptive or non-contraceptive benefits outweigh any unknown potential increase in recurrence risk. (III-C)

### Progestin-Only Oral Contraceptives

The progestin-only pill (POP) is available in Canada as Micronor (supplied in packages of 28 identical tablets, each containing 0.35 mg of norethindrone).<sup>29</sup> POPs are not nearly as widely used as the combined oral contraceptive pills. POPs are most commonly prescribed for breastfeeding women and for women in whom estrogen is contraindicated.

An earlier case-control study from the United Kingdom looking at the use of oral contraceptives in 1176 women with breast cancer and 1176 controls revealed that the same number of women in each group (2.8% and 2.5%, respectively) reported POP use.<sup>43</sup>

The Centers for Disease Control's (CDC) Cancer and Steroid Hormone Study was a case-control study of women

aged 20 to 54 with breast cancer diagnosed between 1980 and 1982.<sup>44</sup> This research, although concentrating on combined contraceptive pills, also addressed the effect of POPs on breast cancer incidence. No overall increased risk of breast cancer was reported.

The UK National Case-Control Study Group examined the risk of breast cancer diagnosed before age 36 and found a marginally decreased risk of 0.85 ( $P = 0.05$ ) per year of POP use after more than 12 months, with a trend of decreased risk with increasing duration of use, based on 123 treated cases and 116 treated controls and a total of 3152 woman-months.<sup>45</sup> This finding lost significance when use within three years prior to diagnosis was excluded. The POPs in the United Kingdom included 0.35 mg of norethindrone as well as 0.50 mg ethynodiol diacetate.

The large meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer looked mostly at breast cancer risk with combined oral contraceptives.<sup>46</sup> Only 0.8% of their study population had used POPs, but the results reported for POPs were similar to those from their overall analysis of all oral contraceptives. There was a non-significant trend to an increase in risk if POPs had been used in the last five years (RR 1.17;  $P = 0.06$ ), but no evidence of increased risk ten years or more after stopping.<sup>46</sup>

It seems unlikely on the basis of the scant data available that use of progestin-only pills is associated with an increased risk of breast cancer overall. The Collaborative Reanalysis raised a suspicion about recent use as a risk factor; however, this concern appears to have been addressed by the UK national case-control study. Even so, progestin-only oral contraceptives expose the user to high levels of progestin, and it would be prudent to avoid their use in breast cancer survivors.

### SUMMARY STATEMENT

3. Although not as well-studied as the combined oral contraceptive pill, POPs do not appear to increase the risk of breast cancer in the general population. (II-2)

### Recommendation

2. Use of POPs in a breast cancer survivor may be considered in a situation where known benefits outweigh any unknown potential increase in recurrence risk. (III-C)

### Contraceptive Implants

The Norplant levonorgestrel implant system is no longer available, but there is a small amount of data regarding risk of breast cancer associated with its use. In a small case-control study<sup>47</sup> there was no evidence of an increased risk associated with Norplant (5 treated cases; 7 controls). Post-marketing surveillance in eight developing countries

involving 7977 women followed for five years (39 337 woman-years of observation) failed to identify any significantly greater risk of breast cancer in Norplant users than in women choosing copper intrauterine devices (IUDs) or surgical sterilization.<sup>47</sup> Benign breast tumours requiring biopsy were also not increased in Norplant users compared with the controls. This report lacks the power and long-term follow-up that would be necessary to demonstrate a small difference in breast cancer risk with Norplant.

Implanon is a single-rod implant that is not yet available in Canada or the United States, but is available in some Middle Eastern and European countries. It releases etonorgestrel, which is an active metabolite of desorgestrel and is the same progestin as in the vaginal ring. Because it is so new, there are no data regarding incidence of breast cancer in past or present users.

### **SUMMARY STATEMENT**

4. There is insufficient evidence to comment on risk or recurrence risk of breast cancer with contraceptive implants in the general population (II-2C) or among breast cancer survivors. (III)

### **LNG-IUS**

There is likewise very little published about risk of breast cancer among users of the LNG-IUS (“Mirena”). The amount of levonorgestrel released is low (20 µg per day) with even less systemic absorption; this device appears to achieve the lowest systemic progestin levels of all the progestin-only methods.<sup>48</sup> One study failed to identify any increased risk in 3416 woman-years of use versus a copper IUD; however, the power was insufficient to detect a small difference in what is certainly a rare event among women of reproductive age.<sup>49</sup> Women were also screened for breast cancer prior to inclusion in the study.<sup>48</sup> Similarly, post-marketing data from Finland found no increase in the number of breast cancer cases from 1990 to 2000 among 17 360 LNG-IUS users when compared with the incidence in the female population as a whole, although the authors acknowledge that there could be confounding factors such as socioeconomic status and parity.<sup>50</sup>

An interesting randomized controlled trial looked at the effect of a LNG-IUS on tamoxifen-stimulated endometrium over 12 months in 122 postmenopausal women being treated for breast cancer.<sup>51</sup> Very little was mentioned in this paper about any possible effect of the low-dose progestin on the recurrence risk of breast cancer. The authors mentioned its primarily local effects with low systemic absorption and felt that it would have a “low risk of an adverse effect on the efficacy of tamoxifen’s action on breast-cancer cells.”<sup>51</sup> Unfortunately, this trial provided

insufficient information about breast cancer recurrence rates over the long term to allow any meaningful conclusions on this issue. As further studies of a potential role for the LNG-IUS in endometrial protection for women on tamoxifen are published, we may be able to gather more information about the device’s effect, if any, on breast cancer recurrence, which could clarify its suitability as a contraceptive for premenopausal survivors.

Breast tenderness can be one of the initial nuisance side effects of the LNG-IUS,<sup>48,49</sup> so it would seem that there is some systemic hormonal effect on the breast, at least in the first few months after insertion when levonorgestrel levels are highest.<sup>52</sup> Accordingly, an effect of the LNG-IUS on breast cancer risk cannot be dismissed at this time.

More data on safety are needed before this device can be recommended as a first-line contraceptive for breast cancer survivors. For some women, however, the contraceptive and non-contraceptive benefits of the LNG-IUS could justify its use. In the latest edition of the WHO document “Medical Eligibility Criteria for Contraceptive Use” a comment has been added that “concerns about progression of the disease [breast cancer] may be less with LNG-IUDs than with COCs [combined oral contraceptives] or higher-dose POCs [progestin-only contraceptives]” although they still list the LNG-IUS as “category 4” for women with current or recent breast cancer.<sup>13</sup> No references were given.

### **SUMMARY STATEMENT**

5. The limited data available suggest that the LNG-IUS does not seem to increase breast cancer risk in the general population. (II-2)

### **Recommendation**

3. Use of the LNG-IUS in the breast cancer survivor can be considered if the unique contraceptive or non-contraceptive benefits outweigh the risk of an unknown effect on recurrence. (III-C)

### **CONCLUSIONS**

Most information about breast cancer risk associated with progestin-only contraception has focused on DMPA and the available data are mostly reassuring. Limited data on the POP leave unresolved the question of increased risk linked to recent use; however, the effect, if real, would be very small. There are very few data on implants and the LNG-IUS. There are no data specifically addressing use of progestin-only contraceptives in breast cancer survivors.

As discussed above, basic science data suggest that progestins can have a proliferative and possibly mitogenic effect on breast tissue depending on the timing, type, and

**Table 2. First year failure rates of common contraceptive methods (Adapted from reference 54)**

Method	Unintended pregnancies during the first year of use (%)	
	Typical use	Perfect use
No method	85	85
Withdrawal	27	4
Female condom	21	5
Diaphragm	16	6
Male condom	15	2
Combined hormonal methods: pill, patch, ring	8	0.3
Progestin-only pill	8	0.3
DMPA	3	0.3
Copper IUD (Para Guard)	0.8	0.6
LNG-IUS	0.1	0.1
Tubal ligation	0.5	0.5
Male sterilization	0.15	0.1

DMPA: depot medroxyprogesterone acetate; IUD: intrauterine device; LNG-IUS: levonorgestrel-releasing intrauterine system.

amount of progestin, although experts in the field seem to have contradictory viewpoints on these effects. The complex relationships governing growth and differentiation of breast epithelial tissues are still not fully understood.

For breast cancer survivors, non-hormonal options for contraception should be considered first, including the copper IUD, barrier methods (male and female condom, diaphragm, sponge etc.), and permanent sterilization or natural family planning methods. These methods are described in detail in the SOGC's Canadian Contraception Consensus.<sup>53</sup> Assuming pregnancy is not desired, contraceptive efficacy is paramount in this population for physical and psychosocial reasons, so a copper IUD or sterilization would be most appropriate because of their low failure rates. See Table 2 for failure rates of common contraceptive methods in the general population.

Failure rates for all methods of contraception decrease as fertility declines with advancing age, making methods that may have an unacceptable failure rate for a younger woman appropriate for a woman in her 40s. Since fertility will be further decreased following chemotherapy (assuming it does not cause premature ovarian failure outright), a contraceptive method with a higher failure rate may be acceptable in the small population of women who are still menstruating after treatment for breast cancer.

In circumstances where a progestin-only method such as the LNG-IUS offers unique contraceptive or non-contraceptive benefits, this method may be appropriate as long as the woman understands that available data remain insufficient to provide unequivocal proof of safety. DMPA

and the POP expose the breast to relatively high levels of synthetic progestins and, given the uncertainties about long-term safety in breast cancer survivors, these methods are probably best avoided until more information is available.

Further research focusing specifically on the risks of progestin-only methods in the breast cancer survivor are needed; however, given the small size of the relevant population, as well as the general reluctance by the medical community to prescribe any hormones following treatment for breast cancer, such studies will be difficult to carry out. Research looking at endometrial protection with the LNG-IUS in tamoxifen users may provide further clarification of the effect (or lack thereof) of this system on breast cancer recurrence.

## SUMMARY STATEMENTS

6. Sterilization and the copper IUD are the most reliable non-hormonal contraceptive methods. (II-1)
7. Other non-hormonal methods may also be appropriate given decreased fertility with advancing age and after chemotherapy. (III)
8. Further research into progestin-only contraception in the breast cancer survivor is needed. (III)

## Recommendation

4. Non-hormonal contraceptive methods should be used as first-line options in the breast cancer survivor. (III-C)

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