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Percutaneous Progesterone Use and Risk of Breast Cancer: Results from a French Cohort Study of Premenopausal Women with Benign Breast Disease

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ABSTRACT: Percutaneous progesterone topically applied on the breast has been proposed and widely used in the relief of mastalgia and benign breast disease by numerous gynecologists and general practitioners. However, its chronic use has never been evaluated in relation to breast cancer risk. The association between percutaneous progesterone use and the risk of breast cancer was evaluated in a cohort study of 1150 premenopausal French women with benign breast disease diagnosed in two breast clinics between 1976 and 1979. The follow-up accumulated 12,462 person-years. Percutaneous progesterone had been prescribed to 58% of the women. There was no association between breast cancer risk and the use of percutaneous progesterone (RR = 0.8; 95% confidence interval 0.4-1.6). Although the combined treatment of oral progestogens with percutaneous progesterone significantly decreased the risk of breast cancer (RR = 0.5; 95% confidence interval 0.2-0.9) as compared with nonusers, there was no significant difference in the risk of breast cancer in percutaneous progesterone users versus nonusers among oral progestogen users. Taken together, these results suggest at least an absence of deleterious effects caused by percutaneous progesterone use in women with benign breast disease.

KEY WORDS: benign breast disease, breast cancer, cohort study, progesterone use.

I. INTRODUCTION

The high incidence of breast cancer (BC) in developed countries has stimulated interest in the exploration and validation of methods to reduce the risk of BC. Except for genetic factors, there is some evidence that the most important risk factors for BC act predominantly through hormonal pathways.¹ The relationship between female sex hormones and BC has been evaluated in a considerable number of epidemiological studies. Estrogens have been recognized as one of the key factors involved in mammary carcinogenesis in both animal models and humans.^{2,3} It remains unclear whether progestogens play a role in human breast cell proliferation, and the issue continues to be debated.⁴⁻¹⁰

Based on epidemiological studies, contradictory results have been reported concerning the risk associated with the use of progestogens either alone or combined with estrogens.^{11,12} Progestogens represent a large class of compounds with different potencies. The clinical use of oral progesterone has been limited for a long time because of its rapid hepatic metabolism, limiting the possibility of a sustained action on the target cells. However, the subcutaneous localization of the breast offers the possibility of frequent percutaneous administration, allowing direct access to the breast epithelial cells and bypassing the hepatic metabolism occurring with the oral route.¹³ Therefore, based on both biological arguments and a limited series of patients,¹⁴ topical application of progesterone on the breast has been proposed. It has become

very common, at least in France, as a treatment for breast symptoms such as mastodynia or nodularity score, in spite of the results of a randomized crossover clinical trial versus placebo that did not show any significant beneficial effect on these symptoms.¹⁵ Indeed, this trial was limited in time and power, with an important number of women lost to follow-up (32%). In addition, these studies never addressed the long-term effect of the treatment on BC risk. Since only a long duration of mastalgia or severe pain was found to be associated with a higher risk of BC,^{16,17} it was anticipated that only a long duration of percutaneous progesterone use might be active on BC risk.

In an earlier report we examined the relationship between oral progestogens used alone and BC in a French cohort study of 1150 premenopausal women with benign breast disease (BBD) followed for a 10-year period.¹⁸ Given the lack of studies addressing this specific issue, our cohort study gave us the opportunity to gather some informative data concerning BC risk and percutaneous progesterone use in long-term followed-up women with BBD. The aim of the present study was to evaluate the relation of percutaneous breast progesterone application on the risk of BC in our cohort.

II. MATERIALS AND METHODS

A. Definition of the Population

The design of the study has been described elsewhere.¹⁸ Briefly, the study was conducted in two French hospitals in the Paris area, the Hospital Necker (NH) and the Institut Gustave Roussy (IGR). Patients were considered eligible for the study if they were French-born, 20–50 years old, premenopausal, had a diagnosis of BBD or isolated cyclical mastalgia, had no personal history of breast cancer, no cancer at another site, and did not develop BC within 1 year of the first visit. BBD included nodular hyperplasia, fibroadenoma, fibrocystic disease, isolated cyst, isolated mastalgia, and nipple discharge (excluding galactorrhea) as described by Haagensen.¹⁹ The diagnosis was based on clinical symptoms, breast palpation, and radiologic abnormalities. Additional ultrasonography, cytology, and histologic verifications were performed when necessary.

All consecutive eligible women seen for the first

time in the NH between 1976 and 1979 and in the IGR between 1977 and 1978 were included in the study. The inclusion periods were determined in order to recruit 600 patients in each center.

B. Data Collection

Six specially trained gynecologists were in charge of the management of the study in both centers and filled in the questionnaires. The initial and follow-up interviews were performed by the senior consultant, who reported all relevant information in the patient medical record. The initial questionnaire included information about known and suspected risk factors for BC, the type of BBD, the diagnostic procedure used including the occurrence of biopsy, and past hormonal treatments. The follow-up questionnaires included detailed information on all hormonal treatments used during the interval between two visits, on the main intercurrent events such as pregnancy and the outcome, and the occurrence of menopause, gynecological, and general disorders.

All patients who failed to return to the clinic were contacted by mail. They were asked to complete and return a similar questionnaire. When breast disease occurred, the physician, gynecologist, or surgeon was subsequently contacted to verify the specific diagnosis.

When a patient did not return the questionnaire, two to three new mailings or phone calls were attempted. When a patient moved, the French telematic system of France Telecom was used to obtain the new address. When a patient could not be found, despite several attempts to contact her by mail or phone, her vital status was obtained from the town hall of her birthplace.

C. Classification of Progestogens

The progestogens were categorized according to their type of administration, that is, oral or percutaneous. Oral progestogen use was classified into two categories. The first category concerned 19-nortestosterone derivatives administered at least 15 days per cycle and at antigonadotropic doses. The second one comprised all other compounds such as pregnane or norpregnane derivatives and nortestosterone derivatives at doses and regimens lower than in

the first category. Only natural progesterone (Progestogel®; a natural molecule of progesterone dissolved in an excipient composed of carboxypolyvinyl, triethanolamine, 95% alcohol, and purified water) was used percutaneously. Using a specific graduated ruler, women were told to apply one dose of the substance, that is, 5 g corresponding to 0.05 g of progesterone, on each breast. A woman was noted as a user of percutaneous progesterone if she reported continuous or at least 10 days by cycle of topical use. Severe breast cyclical mastalgia is the principal indication for this use which has been approved by the French National Agency for drug approval.

D. Statistical Methods

The risk of BC was evaluated using the Cox proportional hazards model.²⁰ In the analysis, the follow-up period started at the time of inclusion and ended in December 1990. Death from causes other than breast cancer and prophylactic bilateral mastectomy were considered as censoring events. The main variables in the present analysis were the use of percutaneous progesterone and duration of use. Four potential confounding variables were added to the model: type of BBD (fibrocystic disease versus all other types of BBD); age at the first visit grouped in three categories: <30; 30–39; >40 years old; existence of cyclical mastalgia; and oral progestogen use, such as described above. In addition, as the occurrence of menopause during the follow-up period could potentially modify the risk of BC, the model was stratified on menopausal status. The statistical analysis was performed using the BMDP software.²¹ Tests for statistical significance were based on the regression coefficients and their standard errors. The proportionality of the Cox model was assessed using the 2L BMDP program.

As this cohort study was initially conducted to address the effect of oral progestogen use, and considering both the small number of BC cases observed during the follow-up period and the small number of long-term users of percutaneous progesterone, the power of the study needed to be addressed. It was studied using the methodology proposed by Akazawa et al.²² This methodology does not imply an exponential form for the baseline hazard function and keeps the same counts as the observed data regarding the

total number of events of interest, that is, the occurrence of breast cancer and the censored events between two events of interest. A total of more than 1200 simulated series were computed using the covariate parameters estimated on the observed dataset and the same structure and counts of events and censoring.

III. RESULTS

A total of 1150 women were included. The characteristics of these women have been previously reported.¹⁸ Briefly, their mean age at inclusion was 37.5 years, 24% of the women were nulliparous, and 11% had a family history of BC. During the follow-up period, a total of 12,462 person-years were documented and 44 histologically checked BCs occurred.

The characteristics of ever-users of percutaneous progesterone according to the main covariates are shown in Table I. Percutaneous progesterone was prescribed to 669 patients (58%); 10% were exposed to percutaneous progesterone alone and 48% were exposed to both oral progestogens and percutaneous progesterone. The other characteristics of the patients, such as family history of breast cancer, age at menarche, number of children, age at first full-term pregnancy, did not differ between ever- and never-users of percutaneous progesterone. The mean duration of follow-up for nonusers and ever-users of percutaneous progesterone were 10.3 ± 3.4 and 10.7 ± 3.5 years, respectively.

The adjusted relative risk of breast cancer in ever-users of percutaneous progesterone as compared to never-users was not significantly different from unity (Table II). Table III details the relative risk of BC for ever-users as compared to never-users of percutaneous progesterone. The analysis took into account the overall oral progestogen use and each category of oral progestogen use, that is, 19-nortestosterone derivatives and other progestogens. The association of the percutaneous progesterone and oral progestogens significantly decreased the risk of BC (RR = 0.5; 95% confidence interval 0.2–0.9). Among ever-users of oral progestogens, there was no significant difference in the risk of BC between oral progestogen alone or combined with percutaneous progesterone. Similar results were observed with the use of 19-nortestosterone derivatives and percutaneous progesterone.

TABLE I
Percutaneous Progesterone Use According to the Characteristics of the Patients in the Cohort

Characteristics	Number of women	Ever-users		<i>p</i> ^a
		<i>n</i>	%	
Age at first visit (years)				
20-29	225	155	69	
30-39	373	239	64	
40-50	552	275	50	0.0001
Menopausal status ^b				
No	623	392	63	
Yes	527	277	53	0.0001
Mastalgia at first visit				
No	1036	583	56	
Yes	114	86	75	0.0001
Fibrocystic disease at first visit				
No	554	362	65	
Yes	596	307	52	0.0001
Oral progestogen use				
No	384	110	29	
Yes	766	559	73	0.0001

^a *p* value, test for homogeneity between categories.

^b Menopause occurring during follow-up period.

TABLE II
Relative Risk of Breast Cancer Associated with the Use of Percutaneous Natural Progesterone

Percutaneous progestogen use	Number of women at risk	Number of breast cancer	Relative risk ^a of breast cancer (95% CI)
No	481	22	1 ^b
Yes	669	22	0.8 (0.4-1.6)

^a Relative risk adjusted for age, cyclical mastalgia, type of benign breast disease, and oral progestogen use and stratified on change in menopausal status during the follow-up period.

^b Reference category.

We also studied the effect of duration of percutaneous progesterone use (Table IV). In the total population, neither the decreased risk of BC associated with a duration greater than 3 years nor the test for trend were significant. Similar results were observed in the two subpopulations of women of never- and ever-users of oral progestogens. However, in never-users, only 14 patients used percutaneous progesterone for more than 3 years.

Using the method of stimulation for power analysis as described in the Materials and Methods section,

our study exhibited a power of 85% for rejecting the alternative hypothesis of a significant effect in percutaneous progesterone users as calculated by the Cox model after adjustment on five covariates.

IV. DISCUSSION

In a cohort study of 1150 premenopausal women with BBD, percutaneous progesterone use was not associated with BC risk. However, when the analysis

TABLE III
Relative Risk of Breast Cancer Associated with Percutaneous Natural Progesterone Use According to Oral Progestogen Use

Types of progestogen	Percutaneous progesterone	Number of women at risk	Number of breast cancers	Relative risk ^a of breast cancer (95% CI)	
Any Type	Nonusers	274	15	1 ^b	
	Ever-users	110	5	0.8 (0.3-2.4)	
	Ever-users	Nonusers	207	7	0.6 (0.2-1.4)
		Ever-users	559	17	0.5 (0.2-0.9)
19-nortestosterone derivatives	Nonusers	361	19	1 ^b	
	Ever-users	190	10	1.0 (0.3-2.4)	
	Ever-users	Nonusers	120	3	0.4 (0.1-1.5)
		Ever-users	479	12	0.4 (0.2-0.8)
Other progestogens	Nonusers	344	16	1 ^b	
	Ever-users	333	12	0.7 (0.3-1.4)	
	Ever-users	Nonusers	137	6	0.8 (0.3-2.1)
		Ever-users	336	10	0.5 (0.2-1.2)

^a Relative risk, adjusted for age, cyclical mastalgia, and type of benign breast disease, and stratified on change in menopausal status during the follow-up period.
^b Reference category.

was restricted to the subgroup of oral progestogen ever-users, a slight decrease in BC risk was observed. In contrast, the risk of breast cancer was not significantly modified in never-users of oral progestogen. To our knowledge, this study represents a first attempt at evaluating percutaneous progesterone use in relation to breast cancer risk.

Several factors could have influenced the results of the present study. Thus as percutaneous progesterone has been frequently considered by both physicians and patients as a minor adjuvant and a rather unprecise therapeutic, getting an accurate report of the treatment actually administered remained a difficult task. The cohort design allowed for minimizing, yet not suppressing this source of bias. In contrast to the dichotomic variable, use/no use of percutaneous progesterone, and the global estimation of the extent of time in months when the treatment was taken, it had to be acknowledged that they reflected a broad range of the instantaneous or cumulated doses received, with a large inter- and intra-individual variability, actually corresponding to the clinical practice at least in France. The power of the study to detect any effect is another important issue. The sample size of the cohort was initially based on oral progesterone use.¹⁸ There-

fore conclusions of the present analysis should be interpreted cautiously, especially in the case of non-significant results. However, the power of 85% gives relative confidence in our conclusions of a nonsignificant effect of percutaneous progesterone of BC risk. Another potential source of bias could be due to higher percutaneous progesterone use in women at lower risk of developing BC. However, users and nonusers of percutaneous progesterone did not differ as far as known BC risks, like family history, age at first full-term pregnancy, parity, and age at menarche, were concerned. In addition, the mean duration of follow-up in the user group was slightly higher than in the nonuser group. This would increase the risk should the exposure to the agent be deleterious on breast cancer risk.

Evidence of the biological plausibility of these results remains scarce due to the limited number of studies correlating the breast cytology with the hormonal milieu. Thus interpretation remains ambiguous and still debated.^{7,11,12} However, these *in vivo* experiments, generally designed on a short-term basis, used various indexes of cellularity, the connection of which with the breast cancer risk in long-term exposure remains undescribed. Indeed, more recent data suggest

TABLE IV
Relative Risks of Breast Cancer According to the Duration of Natural Percutaneous Progesterone Use

Duration of percutaneous natural progesterone (months)	Group size	Number of breast cancers	Relative risk ^a of breast cancer (95% CI)
All women			
0	481	22	1.0 ^b
1-36	501	19	1.0 (0.5-1.9)
37+	168	3	0.5 (0.1-1.7)
Never-users of oral progestogens			
0	274	15	1.0 ^b
1-36	96	4	0.6 (0.2-2.0)
37+	14	1	0.7 (0.1-6.5)
Ever-users of oral progestogens			
0	207	7	1.0 ^b
1-36	405	15	1.0 (0.4-1.6)
37+	154	2	0.7 (0.1-1.5)

^a Relative risk of breast cancer, adjusted on age, cyclical mastalgia, type of benign breast disease, oral progestogen use (for "all women"), and stratified on change in menopausal status during the follow-up period.

^b Reference category.

large discrepancies in the cellular effects of progesterone between chronic and intermittent exposures: Musgrove et al.⁹ performed *in vitro* studies demonstrating that breast cells in the late phase of cell cycle activity are initially driven to the S phase of DNA synthesis by progestogens. This transient effect is followed by cell cycle arrest and growth inhibition, then halting the breast cell division in early G1 phase. The authors of these experiments underline a dual effect of progestins according to the duration of their application, which might reconcile both hypotheses for the role of progestogens both stimulator on a short-term basis and inhibitor on a long-term basis on breast cell mitoses. However, caution must prevail when extrapolating the findings from *in vitro* studies on breast cancer cell lines to the situation of noncancerous breast cells *in vivo*.

More recently, the *in vivo* study of Chang et al.²³ reported interesting results concerning percutaneous progesterone. Premenopausal women undergoing plastic surgery for benign mammary lesions received one of four treatments—estradiol gel, progesterone gel, combined progesterone and estradiol gel, or placebo—which were applied on the breast 11-13 days

before surgery. Samples of glandular tissue were collected and the mitotic activity was measured. A lower rate of mitotic activity was found in the progesterone-treated group than in the estradiol-treated group, suggesting that *in vivo*, high intratissular concentrations of progesterone were able to decrease the mitotic activity of the normal lobular epithelial cells. Future *in vivo* longitudinal studies using non-invasive methods could help in clarifying this issue.²⁴

A previous study by our group on the same population showed that oral progestogen use did not increase the BC risk. Furthermore, a significant trend for a reduction of BC risk was observed in the group of 19-nortestosterone derivative users. The present study provides additional information on percutaneous progesterone use and its relation to BC risk. Even adjusting for percutaneous progesterone, the previous results of our cohort study remain unchanged.

Since our dataset corresponded to a very specific population of urban and suburban women with a benign breast disease, extrapolation of the results of a study carried out on a specific population should always be extrapolated to other populations with caution. However, the results of this study suggest, at

least, that the use of percutaneous progesterone in similar populations of women with BBD is nondel-
eterious on the BC risk.

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