5-fold increase in premenopausal BC (post-menopausal diff.) and slight 10-fold increase in deaths from all malignant neoplasms. 1000 women - 30 years

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BREAST CANCER INCIDENCE IN WOMEN WITH A HISTORY OF PROGESTERONE DEFICIENCY

LEON GORDIS,[1] JAMES A. TONASCIA[1,2] AND GEORGEANNA SEEGAR JONES[3]

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In order to investigate the nature of the association of involuntarily delayed first birth and risk of breast cancer, 1083 white women who had been evaluated and treated for infertility from 1945—1965 were followed prospectively through April 1978 to ascertain their breast cancer incidence. These women were categorized as to the cause of infertility into two groups, those with endogenous progesterone deficiency (PD) and those with nonhormonal causes (NH). Women in the PD group had 5.4 times the risk of premenopausal breast cancer compared to women in the NH group. This excess risk could not be explained by differences between the two groups in ages at menarche or menopause, history of oral contraceptive use, history of benign breast disease or age at first birth. Women in the PD group also experienced a 10-fold increase in deaths from all malignant neoplasms compared to the NH group. The incidence of postmenopausal breast cancer did not differ significantly between the two groups.

breast neoplasms; fertility; progesterone

Late age at first birth has been found to be associated with an increased risk of breast cancer in several epidemiologic studies (1, 2). While a late first birth may directly influence breast cancer risk, it has also been recognized that the association of first birth and risk of breast cancer could be an indirect one, with both increased risk of breast cancer and late age at first birth resulting from some underlying hormonal abnormality (2, 3). Ovulatory defects, especially those resulting in inadequate production of progesterone by the corpus luteum, are frequently associated with fertility problems (4). Menstrual cycles which are deficient in the luteal phase also subject the breast to an altered hormonal milieu of persistent estrogenic stimulation (5). Therefore, it has been proposed that the underlying hormonal abnormality which influences both age at first birth and breast cancer risk may be a deficiency of endogenous progesterone production (5).

The present study capitalized on an unusual opportunity to investigate the relationship of the cause of involuntarily delayed first birth and risk of breast

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Abbreviations: NH, nonhormonal group; PD, progesterone-deficient group.

[1] Department of Epidemiology, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, MD.

Reprint requests to Dr. Cowan at current address: Clinical Research Clinic, Population Studies, Oklahoma Medical Research Foundation, 825 N.E. 13th Street, Oklahoma City, OK 73104.

[2] Department of Biostatistics, School of Hygiene and Public Health, The Johns Hopkins University.

[3] Department of Obstetrics and Gynecology, The Johns Hopkins School of Medicine. Present address: Department of Obstetrics and Gynecology, Eastern Virginia Medical School, Norfolk, VA.

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cancer by studying a population of women who had been evaluated and treated for infertility from 1945 through 1965. These women were subsequently followed through April 1978 in order to compare their incidence of breast cancer and to ascertain their post-treatment pregnancy experience. This study was designed to determine whether women with a history of infertility due to deficient endogenous progesterone production had a greater risk of breast cancer than women whose infertility resulted from nonhormonal factors, regardless of their age at first birth.

Methods

Study population. The study group consisted of women who were evaluated and treated for infertility from 1945 through 1965 at The Johns Hopkins Private Obstetrics and Gynecology Clinic. Clinic records of all infertility patients were reviewed in order to identify women who met all of the study's inclusion criteria (table 1). Data concerning results of diagnostic tests, medical history, diagnoses and treatment were collected from the records of all 1083 eligible subjects. Direct measures of hormonal function, such as estriol ratios or pregnanediol levels, were not collected for use in this study since such measurements had not been uniformly done on all patients and laboratory methods had changed over time.

Table 1

Criteria for inclusion as a study participant

Any one of the following diagnoses:
Primary infertility—women who had never conceived.
Secondary infertility—women who had had a maximum of two pregnancies, each of which lasted less than five months.
Habitual (repeated) abortion—women who had had three or more pregnancies, each of which lasted less than five months.
White.
First clinic visit before January 1, 1966.
Maryland resident at the time of the first clinic visit.
No history of pregnancies lasting five months or longer prior to the first clinic visit.
Not pregnant at the first clinic visit.
More than one clinic visit.

Based on the information collected from the subjects' clinical records concerning the cause of infertility, women were divided into two major study groups:

1) Progesterone-deficient (PD) group: women ever diagnosed as having deficient endogenous progesterone production. Classification was based on the results of timed endometrial biopsies, tests of cervical mucus, basal body temperature charts, and the presence of conditions such as luteal phase defects, aluteal cycles or Stein-Leventhal syndrome. = PCO

2) Nonhormonal (NH) group: women whose infertility was not related to hormonal factors. These women were considered to have normal hormonal function on the basis of the same clinical tests and diagnostic data described above. The causes of infertility represented in the nonhormonal group included uterine, cervical, peritoneal and/or tubal factors, genetic factors, or no specific etiologic factors identified (all diagnostic tests normal).

Women were categorized according to the cause of infertility without knowledge of their follow-up responses or survivorship status. Women whose infertility resulted from other hormonal abnormalities such as premature menopause (n = 23) and women who could not be classified due to insufficient diagnostic testing (n = 15) were only included in the analysis of breast cancer incidence by age at first birth, when cause of infertility was not a factor.

Follow-up data collection. The follow-up phase of the study was carried out over a 16-month period which ended in April 1978. Breast cancer incidence, subsequent to the subject's first clinic visit, was ascertained through a mailed questionnaire which dealt with reproductive, menstrual and medical histories. Re-

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peated mailings were supplemented with telephone contacts to maximize responses. The staff who conducted the follow-up phase of the study were not aware of the subjects' classification as to cause of infertility.

Validation of diagnosis. An attempt was made to validate each reported case of cancer by contacting the attending physician and the hospital where the woman was treated. Validation information was obtained for 14 (82 per cent) of the 17 reported breast cancer cases. All 14 cases were confirmed by the attending physician and/or the hospital where the subject reported having been treated. In addition, death certificates were obtained for 26 of the 27 ascertained deaths.

Analyses. Chi-square tests were used to determine whether the distributions of selected characteristics differed in the PD and NH groups. Continuous data such as age were grouped into appropriate intervals (6). Differences in mean values were evaluated by Student's t-test (6). Maximum likelihood estimates of the ratios of mortality and incidence rates in the PD versus the NH group, standardized for age and year of entry into the study, were computed using a log-linear Poisson model (7). The age- and calendar-year-specific rates for the PD and NH groups combined were used as the standard for adjustment. Exact 95 per cent confidence limits on the standardized ratios were calculated according to the method described for determining confidence limits on the ratio of two Poisson variables (8).

The incidence of breast cancer in both the PD and NH groups was also compared to that of the general population, using age- and calendar-year-specific rates from the New York State Cancer Registry (9) and the Connecticut Cancer Registry (10–12) to compute expected numbers of events (13). Ninety-five per cent confidence limits on the ratio of observed to expected events were calculated by treating the observed numbers of events as Poisson variables (14).

Person-years of observation for all women were included in the calculation of mortality rates. Women who were lost to follow-up were withdrawn from the person-years computation as of the date of their last clinic visit. Incidence rates were based only on the person-years of observation in those women for whom follow-up data were available.

Incident cancer cases include cancer deaths if the onset of disease was after the start of the study. The date of first diagnosis was not known for five of the nine women who died of cancer. Thus, when calculating incidence rates, the date of onset for these women was taken to be the date of death. This allowed them to contribute more years of observation to the denominator of the rates than if the earlier date of onset had been known, thereby making the rates very slightly lower than they would have been if exact dates were known.

Breast cancer cases were categorized as either premenopausal or postmenopausal by comparing reported age at menopause and age at diagnosis for each case. Women whose breast cancer was detected at the same age as their reported age at menopause (peri-menopausal onset) were considered to have developed the disease prior to menopause.

Results

Of the 1083 women eligible for study, 878 (81 per cent) were successfully located during the follow-up phase. Of these, 722 (67 per cent) completed the questionnaire, 27 (2 per cent) were deceased and 129 (12 per cent) did not wish to participate in the study.

Women who were traced and those not traced were compared and were not found to differ significantly in age at first clinic visit or cause of infertility. However, more of the women who could not be located had had their first clinic visit dur-

ing the last interval of the study period (i.e., 1960–1965), suggesting that they were probably younger at the time of follow-up and therefore would have contributed few cases of breast cancer to the study. The distribution by cause of infertility of the 722 respondents was identical to that of the 1083 women in the total study group.

Overall mortality. Women in the PD group had a significantly higher (more than threefold) death rate for all causes of death combined compared to that for women in the NH group (table 2). The excess risk of death from all causes among women in the PD group was due largely to a 10-fold excess risk of death from neoplasms. The types and number of neoplasms reported on death certificates were: breast (one), thyroid (one), malignant melanoma (one), colon (two), brain (one), and leukemia (two) in the PD group and leukemia (one) in the NH group. The two groups did not differ significantly in their risk of death from causes other than cancer.

Incidence of cancer. The standardized incidence of all cancer in the PD group was 1.8 times that in the NH group (table 3). However, the confidence limits included the value 1.0 (0.88–4.0).

Incidence of breast cancer. Women in the PD group had 1.8 times the risk of developing breast cancer compared to women in the NH group, but the difference in risk was not statistically significant (table 3). However, when standardized incidence ratios were calculated separately for pre- and postmenopausal breast cancer, the risk of premenopausal breast cancer was 5.4 times greater for women in the PD group than for those in the NH group (table 4). No significant difference in risk of postmenopausal breast cancer was observed between the two groups. The mean age at diagnosis for premenopausal cases was 42.5 years in the PD group and 41.5 years in the NH group. For postmenopausal breast cancer, the PD case was 48 years of age and the mean age at diagnosis in the NH group was 52.6 years.

Women were then categorized by age at first birth on the basis of their post-treatment pregnancy experience. Only women who reported having had pregnancies lasting five months or longer were considered parous. Table 5 shows

TABLE 2

Comparison of the mortality experience of the progesterone-deficient (PD) and nonhormonal (NH) groups

	Cause of death					
	All causes		Neoplasms		All other causes*	
	PD	NH	PD	NH	PD	NH
No. of deaths	19	7	8	1	11	6
Crude rate per 100,000 person-years†	249.8	77.5	105.2	11.1	144.6	66.4
Standardized ratio of rates (PD:NH)	3.3		10.0		2.2	
95% confidence limits on ratio	(1.3–9.1)		(1.3–422)		(0.74–7.2)	

* The other causes of death and number of deaths in each group were: diabetes (2 PD), cardiovascular disease (2 PD, 2 NH), suicide (3 PD, 2 NH), diseases of the digestive system (2 PD, 1 NH) and other (2 PD, 1 NH).

† Based on 7607 person-years of observation in 433 women in the PD group and 9029 person-years of observation in 520 women in the NH group.

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TABLE 3

Comparison of cancer incidence in the progesterone-deficient (PD) and nonhormonal (NH) groups

	All cancers*		Breast cancer	
	PD	NH	PD	NH
No. of cases	21	13†	10	7
Crude rate per 100,000 person-years‡	333.9	182.0	160.0	89.0
Standardized ratio of rates (PD:NH)	1.8		1.8	
95% confidence limits on ratio	(0.88–4.0)		(0.57–5.1)	

* The types of cancer and number of cases in each group were: uterine corpus (2 NH), cervix in situ (2 PD), ovary (1 NH), choriocarcinoma (1 PD), breast (10 PD, 7 NH), thyroid (1 PD, 2 NH), malignant melanoma (2 PD, 1 NH), colon (2 PD), brain (1 PD) and leukemia (2 PD, 2 NH). Cancer deaths are included if the onset of disease was after the start of the study.

† Excludes two cases which were second primaries.

‡ Based on 6355 person-years of observation in 329 women in the PD group and 7374 person-years of observation in 381 women in the NH group.

TABLE 4

Comparison of pre- and postmenopausal breast cancer incidence in the progesterone-deficient (PD) and nonhormonal (NH) groups

	Premenopausal onset		Postmenopausal onset	
	PD	NH	PD	NH
No. of cases	9	2	1	5
Crude rate per 100,000 person-years	141.6	27.1	15.7	67.8
Standardized ratio of rates (PD:NH)	5.4		0.3	
95% confidence limits on ratio	(1.1–49)		(0.01–2.9)	

TABLE 5

Comparison of breast cancer incidence by parity and age at first birth

	Nulliparous (n = 281; PY = 6244)†	First birth <30 years (n = 242; PY = 4735)	First birth ≥30 years (n = 221; PY = 4429)
No. of cases*	6	5	8
Crude rate per 100,000 person-years	114.4	105.6	180.6
Standardized ratio of incidence rates	Ratio	95% confidence limits	
Nulliparous:first birth <30	0.87	(0.28–4.5)	
Nulliparous:first birth ≥30	0.63	(0.18–2.1)	
First birth <30:first birth ≥30	0.72	(0.15–2.0)	

* Two additional cases of breast cancer, whose infertility was due to causes other than progesterone deficiency or nonhormonal factors, are included in these comparisons.

† n = number of women; PY = person-years of observation.

the standardized incidence ratios for breast cancer by age at first birth. The relative risk for nulliparous women was 13–37 per cent lower than that for parous women, while women whose first birth occurred before age 30 experienced almost a 30 per cent reduction in risk of breast cancer compared to women with a later first birth. However, none of these differences were statistically significant.

The relative risk of premenopausal breast cancer in the PD group compared to the NH group was then assessed within each parity-age stratum (table 6). Women in the PD group had consistently higher relative risks of premenopausal breast cancer within each stratum. There were too few cases of postmenopausal breast cancer to allow for a similar comparison.

The risk of breast cancer in the NH group was comparable to that in the general population (table 7). However, the PD group had a relative risk of breast cancer 2.0 to 2.6 times that of the reference populations. Similar results were obtained when the analysis was restricted to

TABLE 6

Comparison of premenopausal breast cancer incidence in the progesterone-deficient (PD) and nonhormonal (NH) groups by age at first birth

	Nulliparous		Parous <30		Parous ≥30	
	PD (n = 165; PY = 1953)*	NH (n = 165; PY = 3094)	PD (n = 116; PY = 2258)	NH (n = 114; PY = 2232)	PD (n = 105; PY = 2101)	NH (n = 101; PY = 2020)
No. of cases	2	1	3	1	4	0
Crude rate per 100,000 person-years	102.4	32.3	132.9	44.8	190.4	0.0
Standardized ratio of rates (PD:NH)	2.8		3.1		∞	
95% confidence limits on ratio	(0.16–186)		(0.24–155)		(0.64–∞)	

* n = number of women; PY = person-years of observation.

TABLE 7

Observed (O) and expected (E) numbers of incident breast cancer cases in the progesterone-deficient (PD) and nonhormonal (NH) groups, using New York State and Connecticut Cancer Registry data as external standards of comparison

	Using New York State Cancer Registry (exclusive of New York City)				Using Connecticut Cancer Registry			
	O*	E†	O:E	(95% CL)‡	O	E	O:E	(95% CL)
PD group (n = 329; PY = 6365)§	10	3.8	2.6	(1.3–4.9)	10	5.0	2.0	(0.95–3.7)
NH group (n = 381; PY = 7374)	7	4.7	1.5	(0.60–3.1)	7	6.3	1.1	(0.45–2.3)

* Observed number of cases.

† Expected number of cases, based on rates from specified source, adjusted for age and calendar year.

‡ Ninety-five per cent confidence limits on ratio O:E.

§ n = number of women; PY = person-years of observation.

cases whose onset was before age 45 years (an approximation of premenopausal disease).

Other comparisons of PD and NH women. As seen in table 8, respondents in the PD and NH groups generally did not differ on the basis of characteristics previously reported to be associated with an increased risk of breast cancer. However, women in the PD group had significantly more pregnancies and more pregnancies lasting five months or longer than did women in the NH group. In addition, PD women tended to be younger at the time of their first clinic visit and at the time of their first term birth.

Discussion

In the present study, women with a history of deficient endogenous progesterone production had a fivefold excess risk of premenopausal breast cancer compared to women without such history. This result is particularly striking since the PD group had fewer nulliparous women and fewer women with a late first birth than women in the NH group and therefore would be expected to be at a lower risk of breast cancer.

Alternative explanations for this observed association were sought by making a variety of comparisons between women in the PD and NH groups. The relationship of deficient progesterone production and increased risk of premenopausal breast cancer does not appear to be due to any difference between the two groups in other previously identified risk factors. The follow-up was conducted without knowledge of the subjects' hormonal

Table 8

Comparison of selected characteristics of questionnaire respondents in the progesterone-deficient (PD) and nonhormonal (NH) groups

Characteristic	PD group (n = 310)	NH group (n = 374)
Menstrual history		
Menarche before age 14 years	76%	80%
Postmenopausal at follow-up	43%	49%
Natural menopause (of those menopausal)	67%	67%
Menopause before age 45 years (of those menopausal)	38%	34%
Marital and pregnancy history		
Age at first marriage		
Mean	22.3	22.9
% <24 years	70%	63%
Age at first birth		
Mean	29.4	30.0
% >34 years (of those parous)*	10%	20%
Gravidity		
Mean*	2.7	1.9
% nulligravida*	20%	34%
Parity		
Mean*	1.7	1.2
% nulliparous*	26%	42%
Other characteristics		
Mean age at follow-up (years)*	46.9	47.8
Mean years of follow-up	19.5	19.3
Education >12 years	43%	44%
Ever used oral contraceptives	20%	20%
Reported lump in the breast	23%	26%

* $p < 0.05$.

status, and the length of follow-up and per cent of women lost to follow-up were comparable in the two groups. In addition, the PD and NH groups did not differ significantly in their risk of cancers other than breast or in their risk of death from causes other than neoplasms.

One possibility, which could not be completely ruled out, is that the difference in risk of premenopausal breast cancer could have been due to the administration of progestational agents, since progesterone deficiency and the therapeutic use of exogenous progesterone or progestogens were highly correlated. However, of the nine women with premenopausal breast cancer in the PD group, two did not receive any progestational agents, and of those treated, only one women received progesterone supplementation for more than six monthly cycles. In view of the minimal exposure in most women, it is difficult to attribute the excess risk of premenopausal breast cancer in the PD group to use of progestational agents.

Age at first birth was not significantly associated with risk of breast cancer in the present study. This may have been due to the fact that there were too few cases of breast cancer to allow for more than a dichotomization of age at first birth into <30 years old and ≥30 years old. However, similar results have also been reported from the prospective study by Bibbo et al. (15). The observation that women in the PD group had consistently higher risks of premenopausal breast cancer compared to women in the NH group within each age-at-first-birth stratum suggests that the underlying cause of a delayed first birth may be independently associated with risk of breast cancer.

Sherman and Korenman (5) have suggested that in the absence of sufficient cyclic progesterone production, the breast is exposed to a continuous, unopposed estrogen stimulus and that under conditions of altered ovarian function, the breast may also be subjected to the products of disordered secretion of numerous ovarian and pituitary hormones. The evidence for a protective role for progesterone is conflicting, however. A number of studies have found no significant differences in serum progesterone or urinary pregnanediol levels when comparing breast cancer cases and controls (16), parous and nulliparous women (17), daughters of breast cancer cases and daughters of controls (18) or breast cancer free Japanese and British women of varying ages (19). However, Kodama et al. (20) found significantly reduced follicular and luteal phase pregnanediol levels in Japanese premenopausal breast cancer cases compared to controls from an urban area. Luteal phase plasma progesterone levels have also been reported to be significantly lower in women with benign breast diseases than in a group of normal controls (21). Bulbrook et al. (22) found significantly lower plasma progesterone levels and a higher frequency of anovulatory cycles in premenopausal women considered to be at high risk of breast cancer when compared with low-risk women. They observed no difference in progesterone levels in postmenopausal women.

In addition to the excess risk of premenopausal breast cancer, women in the PD group also had a 10-fold increase in risk of death from malignant neoplasms. It is not clear why the death rate was higher in the PD group than in the NH group since the incidence rates for all cancers were not significantly different. Differential ascertainment of deaths may have produced the observed difference in cancer death rates. However, this explanation appears unlikely since the follow-up was conducted without knowledge of the subjects' hormonal status and the completeness and intensity of tracing efforts did not differ between the two groups.

If the excess in cancer deaths in the PD group is real, several explanations can be proposed. First, it is possible that women in the PD group tended to develop types of cancers which have higher case fatality rates. However, the data do not support this. Second, cancers occurring in women with altered ovarian function may be, in general, less responsive to treatment and therefore more likely to be fatal. The observation that breast cancer patients with anovular menstrual cycles were less likely to experience a long-lasting tumor regression after oophorectomy than were patients with normal cycles (23) provides some evidence to support this contention.

While the results of the present study suggest that progesterone deficiency may be associated with an increased risk of premenopausal breast cancer, this investigation is one of the first prospective studies of its kind and the numbers of breast cancer cases and cancer deaths were small. Therefore, additional studies in this area will be needed to either confirm or refute the results of the present study and to investigate further the role of altered hormone production or metabolism in the development of both pre- and postmenopausal breast cancer.

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