Association of Stein–Leventhal Syndrome with the Incidence of Postmenopausal Breast Carcinoma in a Large Prospective Study of Women in Iowa

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BACKGROUND. The Stein-Leventhal syndrome (SLS), first described in 1935, is characterized by infertility, hyperandrogenization, and obesity. Because this phenotype represents an aggregation of risk factors for postmenopausal breast carcinoma, and because in general, a hormonal imbalance underlies the disorder, the authors examined the association between self-reported SLS and breast carcinoma incidence in a cohort of 34,835 cancer-free women assembled in 1986 and followed through 1992.

METHODS. All participants were between the ages of 55 and 69 and held a valid Iowa driver's license. A total of 472 women in the cohort (1.35%) reported a history of SLS at baseline. Incident cases of breast carcinoma were identified annually using the State Health Registry of Iowa. Data were analyzed using Cox proportional hazards regression.

RESULTS. During the follow-up period, there were 883 incident breast carcinomas, 14 among women reporting a history of SLS. Women with SLS were more likely than women without SLS to report fertility problems and menstrual irregularities, but there were no significant differences observed regarding body mass index (BMI). Although women with SLS were 1.8 times as likely to report benign breast disease than women without SLS ($P < 0.01$), they were not more likely to develop breast carcinoma (relative risk [RR] = 1.2; 95% confidence interval [CI] = 0.7–2). Adjustment for age at menarche, age at menopause, parity, oral contraceptive use, BMI, waist-to-hip ratio, and family history of breast carcinoma lowered the RR to 1 (95% CI = 0.6–1.9).

CONCLUSIONS. Despite the high risk profiles of some women with SLS, these results do not suggest that the syndrome per se is associated with an increased risk of postmenopausal breast carcinoma. ***Cancer* 1997; 79:494–9.**
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KEYWORDS: breast carcinoma, postmenopausal, Stein-Leventhal syndrome, polycystic ovaries, cohort.

The Stein–Leventhal syndrome (SLS) first described in 1935,[1] is a heterogeneous condition characterized by menstrual irregularities, infertility, hyperandrogenization, obesity, polycystic ovaries, and other factors. Women with SLS tend to have higher than normal levels of luteinizing hormone (LH), estrone, testosterone, and/or androstenedione, and an elevated ratio of LH to follicle-stimulating hormone (FSH).[2–5] The cause(s) of SLS, also known as polycystic ovary syndrome (PCOS) or polycystic ovarian disease (PCOD), are not known. There are various hypotheses for the primary cause and these focus on the ovaries, the adrenal glands, hypothalamus-pituitary function, and abnormalities in insulin action.[2,4–6]

There is strong evidence to suggest that women with SLS are at increased risk for endometrial carcinoma.[5,7,8] However, it is not clear whether SLS puts women at increased risk for breast carcinoma. An increased risk for breast carcinoma is plausible given that the phenotype associated with SLS represents an aggregation of several potential risk factors for postmenopausal breast carcinoma. For example, positive associations with breast carcinoma have been reported in some, but not all, studies of infertility,[9,10] obesity in general,[11–13] and more recently, abdominal adiposity (a high waist-to-hip ratio [WHR]) in particular.[14–17]

The possible association between polycystic ovaries and breast carcinoma has been investigated in at least two previous studies. Coulam et al.[8] reported an increased risk for breast carcinoma (relative risk [RR] = 1.5; 95% confidence interval [CI] 0.75–2.55) among a cohort of pre- and postmenopausal women with chronic anovulation syndrome. The positive association was due primarily to an excess of cases among postmenopausal women. In contrast, Gammon and Thompson[18] found an inverse association between self-reported physician-diagnosed polycystic ovaries and breast carcinoma in a population-based case–control study, the Cancer and Steroid Hormone Study (CASH). The study included women aged 20 to 54, and the authors reported an odds ratio (OR) of 0.52 (95% CI, 0.32–0.87).

To further evaluate a possible association between SLS and breast carcinoma, and to potentially resolve previous conflicting results, the authors examined data from a large prospective cohort study of postmenopausal women. These results have significance both for clinical management of individuals with the syndrome and for elucidating underlying mechanisms of breast carcinoma.

MATERIALS AND METHODS

Data from the Iowa Women's Health Study was used to investigate a possible association between SLS and postmenopausal breast carcinoma. This prospective cohort study was established to identify risk factors for mortality and cancer incidence in women aged 55–69. Details on the methods used in this study have been published elsewhere.[15] Briefly, in January 1986, a questionnaire was sent to 98,029 randomly selected Iowa women, aged 55–69, who held a valid driver's license in 1985. A total of 41,837 women (42.7%) responded to the baseline mail survey and were followed for mortality and cancer incidence through annual record linkage with the State Health Registry of Iowa, part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. The study protocol was reviewed and approved by the Human Subjects Committees of the Universities of Minnesota and Iowa. Incident cases of breast carcinoma included those with International Classification of Diseases for Oncology codes 174.0–174.9. Nonresponders have been previously characterized,[19] rates of breast carcinoma incidence were comparable in responders and nonresponders (RR = 1.01; 95% CI, 0.92–1.12). Vital status for cohort members was determined through record linkage with Iowa death certificates, the National Death Index, and through mailed follow-up questionnaires in 1987, 1989, and 1992. This report is based on follow-up through December 1992.

Data from a self-administered questionnaire at baseline in 1986 were used for these analyses and include self-reported information regarding reproductive history, menstrual history, history of benign breast disease (BBD), oral contraceptive use (OC use), hormone replacement therapy (HRT) use, family history of breast carcinoma, WHR, and body mass index (BMI) (ratio of weight in kilograms to height in meters squared). Data on weight was collected for current weight as well as at age 18, 30, 40, and 50 years. A history of SLS was determined through the question, ''Have you *ever* been told by a doctor that you have polycystic ovaries (Stein–Leventhal syndrome)?'' Information was not available on either age of diagnosis of SLS or any therapy received.

The hypotheses were formulated to examine SLS and other risk factors for incident breast carcinoma in postmenopausal women with no prior diagnosis of cancer. Therefore, using baseline information, the following criteria were used to exclude women from the analyses: premenopausal (n = 569), prior total or partial mastectomy (n = 1870), history of cancer (other than skin carcinoma) (n = 2293), SLS status unknown (n = 874) or missing (n = 447), and missing information on infertility (n = 991). After exclusions, there were 34,835 women in the at-risk cohort. During 7 years of follow-up, there were 883 incident cases of breast carcinoma.

Factors associated with SLS were evaluated by contingency tables (chi-square test) or Student's *t* tests Person-years of follow-up were tabulated for each subject and incidence data were analyzed using Cox proportional hazards regression to calculate relative risks and 95% CI. Analyses were performed using SAS.[20]

RESULTS

The distribution of selected risk factors for postmenopausal breast carcinoma are presented by self-reported history of SLS in Table 1. Among the at-risk cohort, 472 women (1.35%) reported a history of SLS. The percentage of women who reported that their

TABLE 1
Mean Values (or %) and ± Standard Error of the Mean of Selected Risk Factors for Postmenopausal Breast Carcinoma According to Self-Reported Stein–Leventhal Syndrome Status

	SLS		
Risk factor	**Yes (n = 472)**	**No (n = 34,363)**	***P* value**
Infertility (%)[a]	27.5 ± 0.02	15.6 ± 0.002	< 0.01
Mean no. of pregnancies	3.6 ± 0.11	3.9 ± 0.01	< 0.01
Mean no. of live births	2.7 ± 0.09	3.1 ± 0.01	< 0.01
Mean age at first pregnancy	22 ± 0.20	22.6 ± 0.02	< 0.01
Mean age at menarche	12.8 ± 0.07	12.9 ± 0.01	0.68
Menstrual regularity			
Always	33.2 ± 0.02	45.2 ± 0.003	< 0.01
Usually	44.9 ± 0.02	44.5 ± 0.003	0.85
Never	21.9 ± 0.01	10.4 ± 0.002	< 0.01
Mean age at menopause	43.1 ± 0.3	47.9 ± 0.03	< 0.01
Natural	49.5 ± 0.50	50 ± 0.04	0.30
Surgical	40.9 ± 0.30	42.9 ± 0.05	< 0.01
Menopause (%)[b,c]			
Natural	25.4 ± 0.02	68.3 ± 0.003	< 0.01
Surgical	73.9 ± 0.02	29.7 ± 0.003	< 0.01
Mean body mass index (kg/m^2)	27.2 ± 0.23	27 ± 0.03	0.42
Mean waist-to-hip ratio	0.844 ± 0.004	0.838 ± 0.0005	0.11
Benign breast disease (%)	29.6 ± 0.02	18.8 ± 0.002	< 0.01
Family history of breast carcinoma (%)	13.2 ± 0.02	12.1 ± 0.002	0.46

SLS: Stein–Leventhal syndrome.

[a] Tried for 1 year or more to become pregnant without success.

[b] Approximately 0.5% of women without Stein–Leventhal syndrome (SLS) reported menopause due to use of medication and 1.5% due to ''other'' cause; 0.7% of women with SLS reported menopause due to other cause.

[c] Percentages may not equal 100% due to rounding.

menstrual cycles were ''usually regular'' was essentially the same in women with and without SLS. However, as expected, when compared with women without SLS, fewer women with SLS reported that their cycles were ''always regular'' (45.2% vs. 33.2%, respectively; $P < 0.01$) and more women indicated that their cycles were ''never regular'' (10.4% vs. 21.9%, respectively; $P < 0.01$). Women with SLS were twice as likely as women without SLS to report fertility problems (27.5% vs. 15.6%; $P < 0.01$), and correspondingly, had statistically significantly fewer pregnancies (3.6 vs. 3.9; $P < 0.01$) and live births (2.7 vs. 3.1; $P < 0.01$). Age at first pregnancy was slightly lower in women with SLS. The difference in age at menarche in the 2 groups was not statistically significant, but age at menopause was lower in the SLS group (43.1 years vs. 47.9 years; $P < 0.01$), and probably reflects the fact that this group was also more likely to report surgical menopause (73.9% vs. 29.7%). No significant differences were observed regarding mean BMI; neither current BMI nor BMI at younger ages were different between the two groups (data not shown). However, there was a suggestion of a higher WHR with SLS (0.844 vs. 0.838; $P = 0.11$).

TABLE 2
Age- and Multivariate-Adjusted Relative Risks of Postmenopausal Breast Carcinoma Associated with Self-Reported Stein–Leventhal Syndrome

History of SLS	No. of cases	Person-years	RR[a] (95% CI)	RR[b] (95% CI)
No	869	225,470	1	1
Yes	14	3,084	1.2 (0.7–2)	1 (0.5–1.8)

SLS: Stein-Leventhal syndrome; RR: relative risk; CI: confidence interval.

[a] Adjusted for age.

[b] Adjusted for age, age at menarche, age at menopause, age at first pregnancy, parity, oral contraceptive use, hormone replacement therapy use, body mass index, waist-to-hip ratio, benign breast disease, and family history of breast carcinoma.

Women with SLS were 1.8 times as likely to report a history of benign breast disease (29.6% vs. 18.8%; $P < 0.01$), but they were not at increased risk for breast carcinoma. The age-adjusted RR for breast carcinoma among women with a history of SLS was 1.2 (95% CI, 0.7–2), compared with women without SLS (Table 2). Multivariate adjustment for additional risk factors for breast carcinoma (age at menarche, age at meno-

pause, age at first pregnancy, parity, OC use, HRT use, BMI, WHR, BBD, and family history of breast carcinoma) lowered the RR to 1 (95% CI, 0.5–1.8) (Table 2). A model run without BBD, age at first pregnancy, or use of HRT as covariables yielded the same RR.

SLS is a heterogeneous syndrome; therefore, in an effort to determine if there were risk factors that distinguished women with SLS who went on to develop breast carcinoma from those with SLS who did not develop breast carcinoma, the frequencies of risk factors (specifically, those listed in Table 1) were compared between these groups. The differences observed were consistent with the differences observed between breast carcinoma cases and noncases in women without SLS, except for a self-reported history of BBD. Among women without a history of SLS, 25.9% of those who developed breast carcinoma and 18.6% of those women who did not had reported a history of BBD. In contrast, 28.7% of women with SLS but free of breast carcinoma reported a history of BBD, whereas 61.5% (8 of 13) of the women with both SLS and breast carcinoma had reported a history of BBD.

It has been reported that the association between breast carcinoma and PCOS varies by infertility status.[18] Therefore, additional analyses were performed to examine the effect of infertility in this study. Among women with SLS, the age-adjusted RR of breast carcinoma in women who reported a history of infertility versus those who did not was 1.1 (95% CI, 0.3–3.3). In these analyses, 130 women reported both SLS and infertility, and 4 cases of breast carcinoma occurred among these women during follow-up, whereas 342 women reported having SLS without infertility and 10 cases of breast carcinoma occurred within this group. A comparison was also made to determine if women who reported both SLS and infertility were at increased risk of breast carcinoma compared with women without either condition. The age-adjusted RR was somewhat elevated (1.3; 95% CI, 0.5–3.5), but not statistically significant. This RR was based, again, on 130 women reporting both infertility and SLS with 4 incident cases occurring during follow-up compared with 725 incident cases among 28,991 women reporting no history of either condition.

DISCUSSION

Despite the high risk profile, SLS was not associated with an increased risk of postmenopausal breast carcinoma in this population-based cohort; the age-adjusted RR was 1.2. The RR of breast carcinoma was unity after adjustment for age at menarche and menopause, parity, OC use, BMI, WHR, and family history of breast carcinoma. Further adjustment for BBD, age at first pregnancy, and HRT did not alter the RR.

It might be argued that the inclusion of additional risk factors for breast carcinoma in this multivariate model is statistical overadjustment. Clearly, it is difficult with a disorder of this kind to be certain that one does not adjust for factors that may be on the causal pathway between SLS and breast carcinoma. For instance, if SLS conferred a modest increased risk for breast carcinoma, it could be through obesity. If instead, it were protective, it may be through a lower mean age at menopause (earlier oophorectomy). None of the simpler models that the authors examined revealed marked differences in RRs from the multivariate models. Thus, the current data suggest that SLS is not a risk factor for breast carcinoma, either independently or via known risk factors. The finding that more women with SLS reported a history of BBD was unexpected. This may reflect increased medical surveillance that could accompany women who were diagnosed (and likely treated) for SLS. Consistent with this possibility are the data on mammography use in this cohort; 64.9% of women without SLS reported ever having a mammogram versus 69% of the women with SLS, but the difference was not statistically significant. More medical surveillance in this group might yield breast carcinomas diagnosed at an earlier stage as well. Data were available on the size of the breast tumors; the mean size in women with SLS was 18.6 mm versus 21.2 mm in women without SLS; again, this difference was not statistically significant.

At least two previous reports have examined the possible association between SLS and breast carcinoma. The design of the current study differs from these earlier reports in several important respects. Gammon and Thompson,[18] also using self-reported data, observed an inverse association in the CASH study derived from data on women younger than age 55. Coulam et al.[8] examined the risk of breast carcinoma in a retrospective cohort of women seen at the Mayo Clinic. Women were included in the study if it was determined by medical record review that they had chronic anovulation syndrome (surgical evidence from ovaries [gross appearance or pathology specimen] of SLS, or chronic anovulation with evidence of estrogen production). The investigators found 5 cases of breast carcinoma versus 1.4 expected cases (RR = 3; 95% CI, 1.2–8.3) in a postmenopausal subgroup, but no marked alteration in risk in peri- or premenopausal women. The current study was large, population-based, and prospective. It examined postmenopausal women and relied on self-reports. There were 883 incident cases of breast carcinoma, with 14 occurring among women reporting a history of SLS at the time of these analyses.

No association between SLS and breast carcinoma

was observed in the current study and calculations of study power allowed for the exclusion of RRs > 1.7 or <0.59 with 80% power. However, the heterogeneity of the syndrome itself, at both the clinical and biochemical level, and differences in the criteria used to diagnose the condition, may make a true association between some particular characteristic of SLS and breast carcinoma in this and other studies difficult to detect.[3,6,7] Access to medical care and reasons for seeking treatment also vary and probably lead to underdiagnosis of SLS. These difficulties are compounded by a lack of comprehensive information regarding the natural history and population prevalence of SLS.[6] It is not known, for example, if and to what degree the condition is permanent or transient.[4,6] The authors are unaware of any studies that have directly tried to determine the prevalence of SLS. Previous studies using ultrasound to address the question of population prevalence of polycystic ovary morphology (a component of SLS, but not exclusive to or definitive for the disorder),[21] have suffered from either low response rates,[22,23] or biased ascertainment of cases.[24]

Based on case information in published reports, Young and Goldzieher[3] illustrated that even the most common clinical features associated with SLS (e.g., obesity, hirsutism, infertility, and amenorrhea), are not shared by all individuals and that various combinations of these characteristic symptoms are the norm among SLS patients. A diagnosis of SLS can be based on pathologic evidence from an ovarian biopsy or gross appearance of the ovaries. More recently, ultrasound detection of features that identify polycystic ovaries (size and evidence of cysts) in conjunction with clinical symptoms (such as amenorrhea or oligomenorrhea) has also been used.[21] In addition, clinical features with evidence of hormonal imbalance (e.g., elevated LH or LH/FSH or estrogen abnormalities) can lead to a diagnosis of this syndrome.[3,5,7,8,21]

Misclassification on exposure status (i.e., SLS) is recognized to be a potential source of bias in other studies and probably in this study. In the current study, 874 women were unsure about whether or not a physician had ever told them that they had SLS; an additional 447 women had data missing on this question and were excluded from the analyses. This is of concern, but it is most likely that these women did not represent false-negative responses; it is unlikely that their exclusion at baseline significantly altered the results. It is possible that the question on SLS itself may have caused some confusion, because polycystic ovaries alone do not constitute SLS; the terms PCOS or PCOD (versus polycystic ovaries) tend to be used synonymously with SLS. It is probable that there are many women in this cohort in whom SLS was undiagnosed; the most likely effect on the RR would be a bias toward unity. However, the self-reported information was assessed at baseline, prior to the diagnosis of breast carcinoma, and therefore would not be subject to the bias of differential recall between cases and noncases of breast carcinoma that might occur in a retrospective study.

The authors did not validate the self-reports of SLS or infertility. However, Gammon and Thompson[25] found that the use of the self-reported data on infertility attributed to polycystic ovaries or SLS yielded an OR for breast carcinoma comparable to that obtained with physician-verified data. The frequencies of self-reported polycystic ovaries/SLS (1.35%) and infertility among SLS individuals (27.5%) in this study are similar to those reported among the population-based controls of the CASH study[18]: 0.94% reported physician-diagnosed polycystic ovaries or SLS, and 27.2% of those with SLS reported a history of infertility (defined as ''unsuccessful attempts to get pregnant for two or more years'').

Farquhar et al.[23] have suggested that women with SLS represent one end of a spectrum that ranges from women with normal ovaries and no clinical disorders at one end to women with polycystic ovaries and associated infertility and endocrine disorders at the other. They further suggest that it is only the women who are severely affected who are referred for clinical treatment. This may explain, in part, differences between population-based estimates of 20% for polycystic ovary morphology diagnosed by ultrasound versus estimates of PCOS prevalence of 1.35% and 0.94% observed in the Iowa and CASH studies, respectively.

Gammon and Thompson[25] found that among women who reported a history of SLS, infertility was associated with an increased risk of breast carcinoma (OR = 5.53). However, a further analysis comparing women with a history of SLS and infertility with those without either yielded an OR for breast carcinoma of 1.11. In the Iowa study, infertility was not associated with breast carcinoma among the SLS cases (OR = 1.1), and a comparison of women with both SLS and infertility with women without either condition did not provide strong evidence for an increased risk for the disease (age-adjusted RR = 1.3; 95% CI, 0.5–3.5). However, these stratified analyses yield four cases in one cell and the data must be interpreted with caution.

SLS has been shown to be associated with an increased risk for endometrial carcinoma in a number of studies.[5,7] Whether or not the association is present in the Iowa Women's cohort is of interest; however, there are not as yet a sufficient number of endometrial carcinomas available for such an analysis.

Despite the high risk profile of some women with

SLS, the current study results do not suggest the syndrome is associated with increased risk of postmenopausal breast carcinoma. The diversity of characteristics that comprise this syndrome may obscure true relationships with disease. It may be that a subset of women with SLS who have a specific hormonal profile (e.g., increased unopposed estrogens) are at increased risk for breast carcinoma, whereas another subset have reduced risk. Future research through molecular epidemiology may be the best approach to resolving this question.

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