Prophylaxis of Spontaneously Developing Mammary Carcinoma in C3H/HeJ Female Mice by Suppression of Prolactin

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SUMMARY

Daily treatment for 1 year of young nulliparous C3H/HeJ mice with 2-bromo-α-ergocryptine (CB-154), an efficacious inhibitor of prolactin secretion, markedly suppressed mammary hyperplastic alveolar nodular development and virtually eliminated the appearance of mammary tumors. Mature multiparous C3H/HeJ mice treated similarly also had reduced numbers of hyperplastic alveolar nodules and decreased mammary tumor incidence, but the response to the ergot was not as striking as that observed in the younger nulliparous mice. 2-Bromo-α-ergocryptine treatment was, however, generally ineffective in promoting regression of palpable mammary tumors in mature multiparous C3H/HeJ mice. Treatment with 2-bromo-α-ergocryptine had no significant effect on pituitary, ovarian, uterine, adrenal, or body weight, nor did it alter the estrous cycles.

The results of this study suggest that prolactin is an important, perhaps essential, hormone in the developmental phases of mouse mammary tumorigenesis. However, this hormone is of considerably less importance in the more advanced stages of the disease. Upon the establishment of the hormone as a prerequisite for the development of human breast cancers, the use of appropriate drug-mediated hormone suppression as a prophylactic treatment for the disease may become feasible.

INTRODUCTION

It is widely recognized that the developmental stages of mammary tumorigenesis in lower animals and humans are influenced markedly by hormones from the pituitary and ovary. Mammary tumor incidence is reduced significantly and influentially by hormones from the pituitary and ovary in mice or rats which were either hypophysectomized (29) or ovariectomized (11, 22, 37) at a relatively young age. Conversely, chronic administration of pituitary or ovarian hormones to mice or rats results in a sharp increase in mammary tumor incidence (4, 8, 16, 20, 31, 44). Similarly, breast tumors are reported relatively early in women ovariectomized relatively early in life (12, 17), and the incidence of these tumors is reported to be increased in humans chronically treated with steroid hormones (1, 2).

As these tumors develop and grow, they may lose their hormonal dependence or responsiveness. The vast majority of advanced spontaneous mammary carcinomas in mice do not respond to changes in the hormonal environment, i.e., the tumors continue to grow after the hosts are either hypophysectomized (30) or ovariectomized (3). In women, approximately 60 to 70% of the malignant breast tumors are not responsive to hormonal chemotherapy or to endocrine ablative treatments (15, 40). Unfortunately, the breast cancers that are hormone responsive are affected only temporarily by these treatments; cure is rarely obtained (15, 40). It seems probable, therefore, that hormonal management of breast tumorigenesis might be considerably more effective if directed toward prevention rather than treatment of existing breast neoplasms.

In recent years, several laboratories have been engaged in evaluating the role of pituitary prolactin in murine mammary tumorigenesis (14, 16, 19, 26, 31, 34, 47, 50). It is clear from these investigations that prolactin plays an important role in the development and growth of these tumors. Thus, chronic injections of prolactin into mice (4) or treatments which increase blood levels of prolactin in mice or rats, e.g., transplantation of multiple pituitaries (31, 44) or placement of hypothalamic lesions (5, 46), result in a markedly higher incidence of mammary tumors.

The control of prolactin secretion is under the predominantly inhibitory influence of the hypothalamus mediated by a neurohormone, prolactin-inhibitory factor (28). Drugs that suppress hypothalamic activity (e.g., reserpine or chlorpromazine) or that enhance hypothalamic activity (e.g., L-dopa3) increase or decrease, respectively, the secretion of prolactin (27). In accord, reserpine has been reported to increase the incidence of mouse mammary tumors (21) and promote growth of rat mammary tumors (45), and L-dopa has been shown to induce regression of rat mammary tumors (27). Recently, several ergot alkaloids (e.g., ergocornine and CB-154) have received considerable attention because of their ability to suppress prolactin secretion by apparently acting both at the hypothalamic (49) and pituitary (23, 48) levels. These ergots appear to mimic the activity of the prolactin-inhibitory factor, i.e., they appear to be specific for prolactin (27, 50) and are efficacious inhibitors of prolactin secretion, not only in mice and rats (23, 48—50), but in humans as well (9, 24, 33). They are also effective in promoting regression of carcinogen-induced rat mammary tumors (6, 18, 38).

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2 NIH Research Career Development Awardee CA-35027.

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3 The abbreviations used are: L-dopa, 3-(3,4-dihydroxyphenyl)-alanine; CB-154, 2-bromo-α-ergocryptine; HAN, hyperplastic alveolar nodules.
The purpose of this investigation is to determine the effects of ergot-induced prolactin suppression on the development of spontaneously occurring mammary carcinoma in C3H/HeJ female mice. More specifically, our purpose is to determine whether or not subnormal levels of this hormone during early normal mammary gland development will interfere sufficiently with the neoplastic process, consequently preventing the subsequent development of mammary carcinoma.

MATERIALS AND METHODS

All animals used in this study were C3H/HeJ female mice obtained from the Jackson Laboratories, Bar Harbor, Maine. They were housed in a temperature- (75 ± 1°F) and light-controlled (14 hr/day) room and provided a diet of Wayne Lab Blox (Allied Mills, Inc., Chicago, III.) and water ad libitum.

Treatment of Young Nulliparous Mice for 1 Year with CB-154. Ninety 2-month-old mice were given s.c. injections (daily for 1 year) of 0.1 mg CB-154 suspended in 0.9% NaCl solution. The CB-154 suspension (1 mg/ml; supplied through the courtesy of Dr. Richard L. Elton, Sandoz Pharmaceuticals, E. Hanover, N. J.) was prepared by dissolving the drug initially in a minimal amount of ethanol and diluting to volume with 0.9% NaCl solution. Ethanol constituted 2.5% or less of the final suspension. A 2nd group of ninety 2-month-old mice, given s.c. injections of the 0.9% NaCl solution-ethanol mixture (daily for 1 year), served as controls. Estrous cycles were determined on the CB-154-treated and control mice 11 to 12 months after the onset of treatment.

One year after the initiation of treatment and 24 hr after the last injection, 10 mice from each group were sacrificed. Ovaries were excised, weighed, and fixed in Bouin's fluid for histological evaluation. Inguinal mammary glands were excised, spread flat on cork, fixed in 15% formalin, and stained for wholemount evaluation by a standard procedure (32).

RESULTS

Treatment of Young Nulliparous Mice for 1 Year with CB-154. Twenty 8-month-old mice (retired breeders) were given s.c. injections of 0.1 mg CB-154 daily for 30 days. Forty 8-month-old mice served as controls; 20 were sacrificed at Day 0 and 20 were sacrificed at Day 30. The controls (Day 30) were given daily injections of the diluent (0.9% NaCl solution-ethanol) only. Twenty-four hr after the last injection, the mice were sacrificed. Mammary glands were excised and evaluated for development and number of HAN as previously described. Twenty mice (controls, Day 0) were sacrificed at the beginning of the treatments for the purpose of determining the number of existing HAN in the mammary gland and the degree of mammary gland development at onset of treatment.

Treatment of Mature Multiparous Mice for 30 Days with CB-154. Twenty 8-month-old mice (retired breeders), free of palpable mammary tumors, were given daily s.c. injections of CB-154 for an initial 7-week period and, subsequently, for 30-day periods at bimonthly intervals for 1 year. Seventy 8-month-old mice, similarly treated, but with diluent only, served as controls. All mice were weighed weekly and examined for mammary tumors at monthly intervals from onset of treatment. At 19 months of age, and 24 hr after the last 30-day treatment period, all surviving mice were sacrificed. Pituitaries, uteri, ovaries, and adrenals were excised and weighed. Inguinal mammary glands were excised and evaluated for development and number of HAN, as described previously.

Treatment of Mature Multiparous Mammary Tumor-bearing Mice for 4 Weeks with CB-154. Seven mature mice (retired breeders) of widely varying ages, each bearing a single spontaneous mammary tumor 1 to 2 cm in diameter, were given s.c. injections of CB-154 daily for 4 weeks. The dose of CB-154 during the 1st week was 0.1 mg/mouse/day and, during the 2nd through 4th weeks, was 0.2 mg/mouse/day. Mammary tumors were measured at their largest diameter with a vernier caliper once weekly.
Prophylaxis of Mammary Tumorigenesis

Table 1

Effects of treatment (1 year) of young C3H/HeJ nulliparous mice with CB-154 on degree of mammary gland development and number of mammary hyperplastic nodules

All mice were treated daily for 1 year, beginning at 2 months and terminating at 14 months of age (no treatment from 14 to 24 months of age). Dose of CB-154, 0.1 mg/mouse/day; controls were treated with 0.9% NaCl solution.

<table>
<thead>
<tr>
<th>Mice</th>
<th>No. of mice examined</th>
<th>Mean inguinal mammary gland development</th>
<th>No. of hyperplastic nodules in inguinal mammary glands</th>
<th>Mice free of hyperplastic nodules in inguinal mammary glands</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14 mo.</td>
<td>24 mo.</td>
<td>14 mo.</td>
<td>24 mo.</td>
</tr>
<tr>
<td>Controls</td>
<td>90</td>
<td>10</td>
<td>16</td>
<td>3.6$^c$</td>
</tr>
<tr>
<td>CB-154-treated</td>
<td>90</td>
<td>10</td>
<td>15</td>
<td>1.0$^c$</td>
</tr>
</tbody>
</table>

$^a$ At beginning of study.
$^b$ At end of study.
$^c$ p < 0.001; controls/CB-154-treated animals.
$^d$ Mean ± S.E.

Day 0 or Day 30 of treatment. Less alveolar development also was noted in the mammary glands of the CB-154-treated mice. The ergot treatment did not affect body weight significantly.

Treatment of Mature Multiparous Mice for 1 Year with CB-154: Effect on Normal, Hyperplastic, and Tumorous Mammary Development. Daily treatment of mature multiparous mice with CB-154 at bimonthly intervals for 1 year significantly (a) suppressed mammary gland development (Table 4), (b) inhibited HAN formation (Table 4), and (c) reduced the incidence of mammary tumors (Chart 2). The mammary glands of the CB-154-treated animals were generally atrophic but still contained a relatively large number of HAN. However, significantly fewer of these nodules were found in CB-154-treated mice, compared with controls. Fifty-one % (36 of 70) of the controls developed mammary tumors during the treatment period, in contrast to 13% (9 of 70) of the CB-154-treated mice. The ratio of mice in each group at 0, 3, 6, 9, and 12 months after onset of treatment was (controls/CB-154-treated) 70/70, 49/32, 44/27, 25/23, and 14/18, respectively.

Treatment of Mature Multiparous Mammary Tumor-bearing Mice for 4 Weeks with CB-154: Effect on Mammary Tumor Growth. Daily treatment with CB-154 of 7 mature multiparous mice, each bearing a single palpable mammary tumor, resulted in regression of only 1 of the 7 tumors. This sole tumor regressed to the point that it was no longer palpable. The remaining 6 tumors grew progressively, and 3 eventually killed the hosts. Body weight was not affected at the 0.1-mg dose (1st week) but was reduced during the 0.2-mg dose schedule (2nd to 4th weeks).

Effect of CB-154 on the Health and Longevity of the Treated Mice. Daily administration of CB-154 to young nulliparous mice had no apparent adverse effects on the health of the animals for the 1st 11 months of treatment. During the 12th month of treatment, all mice (now 13 to 14 months of age) were regrouped into larger cages in order to economize space. This resulted in an immediate marked increase in rate of mouse deaths in both groups but was considerably more striking for the CB-154-treated animals. Concurrent with the
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Table 2
Effects of treatment (1 year) of C3H/HeJ young nulliparous mice with CB-154 on organ weights and length of estrous cycle

All mice were treated daily for 1 year beginning at age 2 months and terminating at 14 months of age (no treatment for 14 to 24 months of age). Dose of CB-154, 0.1 mg/mouse/day; controls were treated with 0.9% NaCl solution.

<table>
<thead>
<tr>
<th>Mice</th>
<th>No. of mice examined at 14 mo.</th>
<th>Body wt (g) at 14 mo.</th>
<th>Pituitary wt (mg) at 24 mo.</th>
<th>Uterine wt (mg) at 24 mo.</th>
<th>Ovarian wt (mg) at 14 mo.</th>
<th>Length of estrous cycle (days) at 13-14 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>90</td>
<td>10</td>
<td>26.5 ± 0.8d</td>
<td>32.1 ± 0.7</td>
<td>10.7 ± 0.2</td>
<td>5.4 ± 0.1e</td>
</tr>
<tr>
<td>CB-154-treated</td>
<td>90</td>
<td>15</td>
<td>27.9 ± 0.7</td>
<td>31.0 ± 1.3</td>
<td>10.2 ± 0.5</td>
<td>5.0 ± 0.1e</td>
</tr>
</tbody>
</table>

Note:
- a At beginning of study.
- b At end of study.
- c Values were derived from 50 controls and 50 CB-154-treated animals.
- d Mean ± S.E.
- e p < 0.01, control/CB-154-treated animals.

Table 3
Effect of treatment (30 days) of mature multiparous C3H/HeJ mice with CB-154 on degree of mammary gland development and number of HAN

All mice were 8 months of age at the beginning of treatment. Controls (Day 0) were sacrificed at the onset of treatment. Controls (Day 30) were treated daily with 0.9% NaCl solution for 30 days. CB-154 (0.1 mg/mouse) was administered daily for 30 days.

<table>
<thead>
<tr>
<th>Mice</th>
<th>No. of mice</th>
<th>Body wt (g)</th>
<th>Mean inguinal mammary gland development</th>
<th>No. of HAN in inguinal mammary glands</th>
<th>Mice free of HAN in inguinal mammary glands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls, at Day 0</td>
<td>20</td>
<td>30.1 ± 1.0a</td>
<td>4.6b</td>
<td>6.0 ± 0.8b</td>
<td>2 10</td>
</tr>
<tr>
<td>Controls, at Day 30</td>
<td>20</td>
<td>30.0 ± 1.0</td>
<td>4.1b</td>
<td>6.6 ± 0.8b</td>
<td>3 15</td>
</tr>
<tr>
<td>CB-154-treated, at Day 30</td>
<td>20</td>
<td>30.0 ± 1.0</td>
<td>2.8b</td>
<td>1.7 ± 0.3b</td>
<td>8 40</td>
</tr>
</tbody>
</table>

Note:
- a Mean ± S.E.
- b p < 0.001, control/CB-154-treated animals.

Table 4
Effects of treatment (1 year) of mature C3H/HeJ multiparous mice with CB-154 on degree of mammary gland development and number of HAN

All mice were treated daily, for 30 days, at bimonthly intervals for a period of 1 year (6 months total treatment). The treatments began when the mice were 8 months of age and ended when they were 19 months old. All mice were sacrificed 24 hr after the last 30-day treatment period. Dose of CB-154, 0.1 mg/mouse/day; controls were treated with 0.9% NaCl solution.

<table>
<thead>
<tr>
<th>Mice</th>
<th>No. of mice</th>
<th>Mean inguinal mammary gland development</th>
<th>No. of HAN in inguinal mammary glands at 19 mo.</th>
<th>Mice free of HAN in inguinal mammary glands at 19 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>70</td>
<td>4.1b</td>
<td>15.9 ± 1.5c</td>
<td>0 0</td>
</tr>
<tr>
<td>CB-154-treated</td>
<td>70</td>
<td>1.8b</td>
<td>10.0 ± 1.4c</td>
<td>1 6</td>
</tr>
</tbody>
</table>

Note:
- a Surviving at end of treatment period.
- b p < 0.001, control/CB-154-treated animals.
- c Mean ± S.E.; p < 0.01, control/CB-154-treated animals.

placement of these mice in new surroundings and with different cagemates was an increase in aggressive behavior, apparently tolerated less well by the ergot-treated mice and presumably, at least in part, the cause of death. As a result, further treatment of both groups was discontinued.

In the mature multiparous mice, our original intention was to treat the mice daily for 12 consecutive months, rather than at bimonthly intervals. After administration of CB-154 daily for 7 consecutive weeks, it was soon apparent that these older animals could not tolerate this dose schedule, since increased...
deleterious effect. In general, young mice are considerably more tolerant of a daily dose of 0.1 mg CB-154 than are older mice. Daily doses greater than 0.1 mg CB-154 for extended periods of time are not tolerated well by either age group. Autopsy of the CB-154-treated animals and the controls revealed no apparent gross differences. Daily treatment of either nulliparous or multiparous mice with CB-154 had no significant effect on pituitary, uterine, ovarian, adrenal, or body weight (Tables 2 and 5).

DISCUSSION

The results of this study demonstrate that mammary tumor incidence is virtually eliminated in young nulliparous C3H/HeJ female mice treated during the early developmental phases of mammary tumorigenesis with CB-154, a known suppressor of prolactin secretion. In mature multiparous mice, suppression of prolactin secretion markedly inhibited but did not totally prevent the development of mammary tumors. In mature multiparous mice bearing palpable mammary tumors, suppression of prolactin secretion was essentially ineffective in promoting regression of these tumors. Concurrent with inhibition of mammary tumor incidence was suppression of HAN development and mammary gland atrophy.

It has been well established by a number of laboratories that hypersecretion of prolactin in mice or rats results in a marked increase in incidence of mammary tumors (4, 5, 16, 31, 44, 46). The results of this study demonstrate that this direct relationship holds true even when prolactin levels are below normal, i.e., that reduced secretion of prolactin during the early developmental phases of the disease results in a striking decrease in incidence of spontaneously occurring mammary tumors. Only 1 of the original 90 mice chronically treated with CB-154 developed a mammary tumor during the 2-year period of this study, and this tumor became palpable 9 months after the discontinuance of drug-induced prolactin suppression. Furthermore, this treatment markedly reduced the number of mammary hyperplastic nodules, an observation consistent with the highly significant decrease in mammary tumor incidence. These results are in accord with the recently published studies of Yanai and Nagasawa (51) and Clemens and Shaar (7), demonstrating that chronic suppression of prolactin secretion inhibited development of induced mammary tumors in mice bearing pituitary isografts (51) and rats treated with 7,12-dimethylbenz(a)anthracene (7). These results suggest that prolactin is extremely important, perhaps essential, in the early developmental phases of both induced and spontaneous murine mammary tumorigenesis.

Thirteen % of the multiparous mice, free of palpable mammary tumors at the beginning of treatment, developed tumors despite suppression of prolactin secretion. Although this incidence was considerably less than that observed in the controls (52%), these results demonstrated that certain populations of mammary tumor cells can grow in a hormonal environment deficient in prolactin. This is further emphasized by the observation that suppression of prolactin secretion was ineffective in inducing mammary tumor regression in 6 of 7 of the multiparous mice already bearing mammary tumors at the onset of treatment. Because mammary tumor-bearing control mice were not used in that phase of the study, it is not known whether the ergot treatment slowed tumor growth. Nevertheless, these results suggest that the advanced palpable mammary tumors, as well as a number of the incipient mammary tumors, in the ergot-treated multiparous mice were prolactin independent. These results do not negate the proposed hypothesis that prolactin may be essential in the neoplastic transforma-

Table 5

<table>
<thead>
<tr>
<th>No. of mice</th>
<th>Effects of treatment at 19 mo. of age</th>
</tr>
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<tbody>
<tr>
<td>Mice</td>
<td>At beginning of study</td>
</tr>
<tr>
<td>Controls</td>
<td>70</td>
</tr>
<tr>
<td>CB-154-treated</td>
<td>70</td>
</tr>
</tbody>
</table>

a Surviving at end of treatment period.
b Mean ± S.E.
tion of the mouse mammary gland. It is important to bear in mind that the multiparous mice underwent several months of normal reproduction prior to induced suppression of prolactin secretion. Ovarian activity and prolactin secretion increase significantly during certain periods of the reproductive cycle, resulting in marked mammary gland stimulation (25). It is probable, therefore, that neoplastic changes in the mammary gland already had occurred prior to the ergot treatment. In support of this inference, 8-month-old multiparous C3H mice have a large number of HAN in their mammary glands as illustrated in this study and as reported by others (3, 10).

Mammary tumor incidence in control nulliparous and multiparous mice was 27 and 52%, respectively, a tumor incidence considerably less than expected for this strain of mouse. The Jackson Laboratories were consulted midway through this study and advised us that their C3H/HeJ strain develops considerably fewer mammary tumors than in previous years, for reasons yet unknown. The mammary tumor incidence reported in the controls of this study is in accord with the incidence currently reported in their laboratories.

There is now ample evidence to demonstrate that HAN antedate mammary tumors in mice and are sensitive to hormones from the pituitary, ovary, and adrenals (3, 10). The results of this study suggest that development and growth of a number of these hyperplasias are dependent upon prolactin. Approximately two-thirds of these hyperplasias were found to have disappeared in 8-month-old multiparous mice treated for 30 days with CB-154. This is in agreement with the recent study of Yanai and Nagasawa (50) who reported significant regression of these lesions in mice treated with ergot alkaloids. However, with time it appears that an increasing number of these hyperplasias become independent of prolactin, as was evident in the large number of these lesions seen in the mammary glands of the older, multiparous mice treated with CB-154. The difference between the number of these hyperplasias in 19-month-old multiparous, ergot-treated mice and in the controls, albeit significant, was not as striking as that observed between 8-month-old multiparous, ergot-treated and control mice. Very few hyperplasias, however, were noted in mammary glands of young nulliparous mice treated with CB-154. Whether or not these hyperplasias are capable of giving rise to a palpable mammary tumor remains to be determined. However, the notable lack of spontaneous mammary hyperplastic outgrowths in these animals suggests that prolactin may be essential in the early phases of mouse mammary oncogenesis.

Recently, a number of ergot alkaloids were shown to be potent suppressors of prolactin secretion. This was suggested first by the studies of Shelesnyak (36) and subsequently confirmed by radioimmunoassay in rats, cows, and man (9, 35, 48) and by disc electrophoresis on polyacrylamide gel in mice (50). Although blood prolactin has not yet been analyzed by radioimmunoassay in ergot-treated mice due to a lack of such an assay for this species, all other mammals thus far treated with CB-154 have shown highly significant suppression of blood prolactin levels by radioimmunoassay. CB-154-treated C3H female mice, however, have pituitary prolactin concentrations considerably less than those of untreated controls, measured by disc electrophoresis on polyacrylamide gel (50). CB-154, compared with other ergots or ergoline derivatives, appears to be one of the most efficacious inhibitors of prolactin secretion in mice, judged by inhibition of mammogenesis, thus far tested in our laboratory (43). There is no evidence to suggest that CB-154 directly interferes with other hormonal processes; that is, it appears to be specific for prolactin. Mice or rats chronically treated with the ergot have normal estrous cycles, suggesting that the drug has no marked inhibitory effect on gonadotrophin secretion (18, 27, 50). Furthermore, growth hormone content of pituitarys of mice treated with CB-154 differs insignificantly from controls (50).

In the present study, mice treated with the ergot had pituitary, ovarian, uterine, and adrenal weights differing insignificantly from the controls and had normal estrous cycles. Only the mammary gland showed marked disparity between control and experimental animals. This is particularly significant since it suggests that mammary tumorigenesis can be blocked even in animals with normal ovarian activity, as long as prolactin secretion is minimal. CB-154 at the dose levels and schedules used in this study did not interfere with normal body weight gains. Drug treatments had no apparent effect on the general health of the animals, with one exception: when the mice were placed in new housing in larger groups, the death rate of the CB-154-treated nulliparous mice initially exceeded that of the controls. The cause of this remains to be determined but may be related to the mild vasoconstrictive activities of natural ergot alkaloids reportedly absent in a number of the synthetic products (41).

The role of prolactin in human breast tumorigenesis is unknown. This is not surprising since only recently has there been sufficient evidence for the singular existence of this hormone in man (13). There is a pressing need to define the relationship of prolactin, as well as ovarian hormones, to development and growth of normal, hyperplastic, and neoplastic mammae in humans. Hyperplastic nodular outgrowths, in some respects similar to that observed in the mouse, have been reported in humans (42), although their hormonal responsiveness is totally unknown. Once these hormonal requirements are known, prophylaxis of the disease may be possible by appropriate drug-mediated hormone suppression.

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