Research Article

Cancer Epidemiology, Biomarkers & Prevention

The GISS Trial: a Phase II Prevention Trial of Screening Plus Goserelin, Ibandronate, versus Screening Alone in Premenopausal Women at Increased Risk of Breast Cancer

Gunter von Minckwitz[1,2], Sibylle Loibl[1], Christian Jackisch[3], Stefan Paepke[4], Caroline Nestle-Kraemling[5], Michael P. Lux[6], Nico Maass[7], Rita Schmutzler[8], Andreas du Bois[9], Diethelm Wallwiener[10], Sabine Vescia[1], Kai Budischewski[11], and Manfred Kaufmann[2]

Abstract

Background: Genetic testing for inherited mutations in breast cancer genes provides valuable information for disease prevention. Today, premenopausal women with increased risk for breast cancer have only limited nonsurgical options to reduce their risk.

Methods: The GISS trial, a randomized, multicenter, open-label phase II trial, assessed the feasibility of a preventive treatment with goserelin and ibandronate for premenopausal women at increased risk for breast cancer. The primary endpoints were refusal to undergo randomization and discontinuation of treatment. Safety and quality of life were also evaluated.

Results: Between the years 2001 and 2003, 31 of 322 eligible women participated in the trial; 15 received goserelin/ibandronate plus screening, 15 screening only, and 1 withdrew her consent after randomization. The treatment duration was 24 months. Here, mainly the results from the first 12 months were evaluated because of the low compliance thereafter. Hot flushes, headache, and vaginal dryness/discharge occurred more often in the goserelin arm. No difference was observed between the two arms in the agreement to randomization, compliance, or any other endpoints.

Conclusions: Acceptance of chemoprevention with goserelin and ibandronate was low. Premenopausal women at increased risk for breast cancer should be better informed about chemoprevention through physician counseling and a more feasible study design (e.g., oral medication) should be provided.

Impact: This is the first chemoprevention trial in premenopausal women at increased risk for breast cancer.
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Introduction

Breast cancer is considered as a family of diseases rather than a single disease; its etiologic aspects can be very diverse. Approximately 5% of breast cancer cases arise due to the mutation of highly penetrating genes, that is, breast cancer 1 (*BRCA1*) and *BRCA2* (1, 2). The identification of breast cancer predisposition gene mutation carriers offered a realistic possibility for early detection and/or preventive strategies.

Prophylactic bilateral mastectomy and/or prophylactic bilateral ovarectomy are current surgical options, which can reduce the risk of breast cancer up to 95% and 50%, respectively (3). Despite the benefits obtained, these surgical approaches would probably be rejected by most women if effective medical options were available (4). The hormonal dependence of breast cancer and the effective endocrine standard treatment with tamoxifen in pre- and postmenopausal women with endocrine responsive disease led to several trials of chemoprevention using tamoxifen. An encouraging reduction of 49% in early breast cancer incidence was reported in the National Surgical Adjuvant Breast and Bowel Project (NSABP) P1 study with 13,388 healthy women older than 35 years when treated with tamoxifen (5). Three other large trials in women aged 30 years or above (6) or 35 years or above (7, 8) also confirmed that tamoxifen chemoprevention resulted in a significant reduction in the incidence of breast cancer.

In all these trials, women younger than 50 years (about 40%) included were mostly at a low or moderate

Authors' Affiliations: [1]German Breast Group, Neu-Isenburg; [2]Universitäts-Frauenklinik, Frankfurt; [3]Klinikum Offenbach GmbH, Offenbach; [4]Universitäts-Frauenklinik, Technische Universität München, Munich; [5]Universitäts-Frauenklinik Düsseldorf, Düsseldorf; [6]Universitäts-Frauenklinik Erlangen, Erlangen; [7]Universitäts-Frauenklinik Kiel, Kiel; [8]Universitäts-Frauenklinik Köln; Köln; [9]Horst-Schmidt-Klinik, Wiesbaden; [10]Universitäts-Frauenklinik Tübingen, Tübingen; and [11]SRH Hochschule Heidelberg, Germany

Corresponding Author: Gunter von Minckwitz, German Breast Group, c/o GBG Forschungs GmbH, Martin-Behaim-Str. 12, 63263 Neu-Isenburg, Germany. Phone: 4969-6102-7480-429; Fax: 4969-6102-7480-440; E-mail: Gunter.vonMinckwitz@germanbreastgroup.de

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breast tumor risk. Until today, no trial on primary chemoprevention of breast cancer only in premenopausal women at increased risk has been published. However, for younger women (≤35 years), a significant family history of breast cancer is a strong predictor for breast cancer development, even stronger than high-risk lesions (9).

Considering the possibility of ovarian suppression in premenopausal women, the application of luteinizing hormone–releasing hormone (LHRH) analogues may represent a valid alternative. Adjuvant trials with more than 3,000 premenopausal breast cancer patients reported a 50% reduction in the risk of developing contralateral breast cancer in women treated for 2 years with LHRH analogues (10). Data from other trials also support the use of LHRH analogues in prevention (11, 12). Some of the disadvantages of the treatment with LHRH analogues in premenopausal women with the subsequent hypoestrogenemia are climacteric symptoms such as bone loss, hot flushes, and vaginal dryness. An approach to prevent the bone loss would be the prophylactic use of bisphosphonates which could prevent osteoporosis and had recently shown a significant risk reduction of relapse in primary breast cancer (13). Therefore, the GISS trial was designed to evaluate the feasibility of the preventive use of a LHRH analogue (goserelin) in combination with bisphosphonate (ibandronate) in premenopausal women at increased risk for breast cancer.

Patients and Methods

Study design

Premenopausal women between 30 and 45 years old with intact ovarian function [follicle-stimulating hormone (FSH) in premenopausal range if not menstruating] and moderate or high genetic risk of breast cancer (risk group criteria are shown in Table 1; ref. 14) were invited to participate in the GISS study, a randomized, multicenter, open-label phase II trial. The participants were randomized to screening only or screening plus treatment. The treatment included a subcutaneous injection of goserelin 3.6 mg once every 4 weeks for 2 years and an infusion of ibandronate 2 mg once every 3 months for 2 years to prevent bone loss. Treatment was started during the last week of the menstrual cycle or the first 3 days of a new cycle. Delays in treatment visits were recorded. No dose or schedule modification was allowed.

Goserelin was supplied as a ready-to-use injection by AstraZeneca GmbH. The ready-to-use injection consisted of 3.8 mg goserelin acetate and 14.2 mg polyglycolic acid plus lactic acid (1:1). Ibandronate was supplied in ampoules by Hoffmann-La Roche AG. The ampoules contained ibandronic acid 1.125 mg (corresponding to 1 mg of ibandronic acid) and monosodium salt.

Approvals from ethics committees were obtained and the study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Table 1. High- and moderate-risk participants' criteria

High-risk participants	Moderate-risk participants
1. *BRCA1* germ line mutation carriers	1. Relatives of an affected female from a family with at least 1 woman with breast cancer and 1 woman with ovarian cancer and an unknown or noninformative *BRCA* status.
2. *BRCA2* germ line mutation carriers	2. Relatives of an affected female from a family with 3 or more women suffering from breast cancer with an age at diagnosis more than 50 years and an unknown or noninformative *BRCA* status in the family.
3. First- or second-degree relatives with a pathogenic *BRCA1* or *BRCA2* mutation.	3. Relatives of an affected female from a family with a single case of breast cancer diagnosed at age 30 years or younger and an unknown or noninformative *BRCA* status in the family.
4. Relatives of an affected woman in a family with at least 2 women suffering from breast cancer under the age of 50 and an unknown, negative, or noninformative *BRCA* status in the family.	4. Relatives of an affected female from a family with 1 woman with bilateral breast cancer at the age of 40 or younger and an unknown or noninformative *BRCA* status in the family.
	5. Relatives of an affected female from a family with 1 woman with breast and ovarian cancer under the age of 40 and an unknown or noninformative *BRCA* status in the family.
	6. Relatives of an affected male from a family with an unknown or noninformative *BRCA* status in the family.

Prior to study participation, each patient gave written informed consent.

Patient eligibility

All participants had to use nonhormonal contraception and must have an estimated *a priori* life expectancy of more than 10 years. Women with the following criteria were excluded: current pregnancy or planning pregnancy in the next 2 years; lactation; current treatment with anticoagulants; history of deep vein thrombosis or pulmonary embolism; and mastectomy.

Endpoints

The primary endpoints were the refusal to undergo randomization and the discontinuation of treatment for any reason. The secondary endpoints were the occurrence of toxicity according to WHO criteria, change in bone mineral density measured by dual-emission X-ray absorptiometry (DEXA) scan every 6 months, change in breast tissues density, breast cancer incidence, and the evaluation of quality of life.

Quality of life was assessed with the state-trait anxiety inventory (STAI) according to Spielberger self-evaluation questionnaire (15) combined with a cancer worry scale at the start of treatment (16), the functional assessment of cancer therapy endocrine symptoms (FACT-ES) evaluation, and a sexual activity questionnaire with categories "not at all," "a little," "somewhat," and "very much."

The STAI self-evaluation questionnaire included the following 20 items: (I feel/am) calm, secure, tense, strained, at ease, upset, worrying over misfortune, satisfied, frightened, comfortable, self-confident, nervous, jittery, indecisive, relaxed, content, worried, confused, steady, and pleasant. The scores of the STAI were defined as: not at all = 1, somewhat = 2, moderately = 3, and very much = 4. The overall anxiety score was calculated as the sum of 20 single scores between 1 and 4. The total scores range from 20 to 80. Higher scores correspond to higher anxiety. The FACT-ES evaluation included 20 items: (I have/am) hot flushes, cold sweats, night sweats, vaginal discharge, vagina itching/irritation, vaginal bleeding or spotting, vaginal dryness, pain or discomfort with intercourse, lost interest in sex, gained weight, lightheaded/dizzy, vomiting, diarrhea, headaches, bloated, breast sensitivity/tenderness, mood swings, irritable, lack of energy, nausea; and the score defined as: not at all = 0, a little bit = 1, somewhat = 2, quite a bit = 3, and very much = 4. The overall symptom score was calculated as the sum of 20 single scores between 0 and 4. The total scores range from 0 to 80. A higher score corresponds to a worse level of symptoms.

Statistical considerations

Blinding was not possible in the GISS trial due to the induction of amenorrhea through goserelin. Randomization was done centrally. Stratification occurred within each participating institution. To select the study population, each site prepared an anonymized list of all women fulfilling the entry criteria. These women were then given a code number and invited to participate in the trial.

Analyses were conducted on an intent-to-treat basis. All participants who were randomized and received treatment or screening were evaluated by treatment arm. Toxicities were graded according to NCI-CTC (National Cancer Institute Common Toxicity Criteria) toxicity scale version 2.0. Repeated measurement ANOVA was conducted to evaluate differences between arms in changes of STAI, FACT-ES, and sexual activity from baseline. Two-sided Fisher's exact test (for binary parameters) was also used to compare the 2 arms.

Results

Recruitment and patients characteristics

Between February 2001 and December 2003, 31 (10%) of 322 invited eligible women had agreed to participate in the GISS trial and were randomized. The 31 participants came from 11 study sites.

The reasons expressed for nonparticipation are summarized in Table 2. The most common reason was fear of anticipated side effects. One participant withdrew her consent directly after randomization.

Thirty participants with a median age of 39.5 years (range: 30–46 years) were equally randomized to the screening only or the treatment arm. Baseline characteristics were well balanced (Table 3). All women were premenopausal, assessed by medical history or by

Table 2. Reasons for not participating in the GISS trial

Reasons	Women (*n*)
Fear of side effects	60
Do not like syringes	47
Natural way of life	37
Clinic difficult to reach	34
Planned pregnancy	15
Reminder of cancer	15
Lack of information	11
Participation in changed study condition	10
Interactions between study medication and other medicine	10
Participation not in pilot phase, maybe in the main study	10
Planned mastectomy	9
Problems with regularity of medicine intake	9
Waiting for BRCA analysis	7
Partner does not agree	6
Unwanted menopause	5
No special reason	3
Pregnant	2
Temporary menopause	1
Total	291

Table 3. Baseline characteristics

	Goserelin + ibandronate ($n = 15$)	Screening only ($n = 15$)
Age, y		
Median (range)	40 (31–46)	38 (30–46)
Mean (SD)	39.6 (4.2)	37.6 (4.3)
Weight, kg		
Median (range)	60 (48–94)	68 (50–94)
Mean (SD)	62.6 (11.2)	69.0 (13.2)
BMI, kg/m^2		
Median (range)	21.6 (19.3–31.4)	24.8 (18.4–30.7)
Mean (SD)	22.5 (3.0)	24.8 (4.0)
Hereditary risk		
Medium	3	2
High	12	13
Age at menarche, y		
Median (range)	13.5 (12–15)	13.0 (10–15)
Mean (SD)	13.5 (0.9)	12.8 (1.4)
Previous oral contraceptive use	14 (93.3%)	12 (80%)
Childbirth	12 (80%)	12 (80%)
Hysterectomy	1 (6.6%)	1 (6.6%)
Gynecologic diseases	4 (26.6%) 1× abortion, 2× uterus myoma, 1× benign breast tumor	4 (26.6%) 1× adnexitis, 2× ovarian cysts, 1× benign breast tumor
Cardiovascular diseases	0	2 (13.3%) 1× nonsymptomatically extra systoles, 1× hypertension

biochemical determination of FSH and luteinizing hormone (LH). Two women in the treatment arm had cardiovascular diseases (hypertension, extrasystoles); no history of cancer, thrombosis, or osteopenia/osteoporosis was reported in any women.

Compliance

Of the 30 participants, 25 completed the first 12 months treatment. The reasons for the 5 discontinuations were pregnancy (1 woman on screening), loss of contact (2 women on screening), or withdrawal of consent without any reason documented (2 women on treatment). No statistically significant difference in the compliance after randomization was observed between the 2 arms.

Only 18 participants completed the 24 months on study with 10 in the treatment arm and 8 in the screening arm. In addition, 8 patients in each arm also completed an additional year of follow-up after the end of the study (Fig. 1).

Because only 18 patients remained in the study for 24 months, mainly the results from the first 12 months were statistically evaluated.

Toxicity

Headache, hot flushes, and vaginal dryness and discharge were more common in the treatment arm than in the screening arm during the 24-month study ($P < 0.05$; Table 4). No statistically significant difference in other toxicities between the 2 arms was observed. Cardiovascular events and bone fractures were also similar in the 2 arms.

Bone density

At baseline, no participant had osteopenia or osteoporosis according to the German Society of Osteology. After 12 months, only 1 woman in the treatment arm showed loss of bone density but no osteoporosis. Accordingly, we did not detect any significant change in bone density after 12 months of treatment with goserelin and ibandronate.

Radiologic breast tissue density

Mammography was done prior to randomization and after 12 months. A reduction of breast tissue density was documented in 1 woman in the treatment arm only. Accordingly, no significant change of breast density was observed after 12 months of treatment with goserelin and ibandronate.

Incidence of cancer

In both arms, no breast cancer event was recorded in any participants over the whole observation period.

Quality of life

STAI. There were no statistically significant differences between the screening and the treatment arm

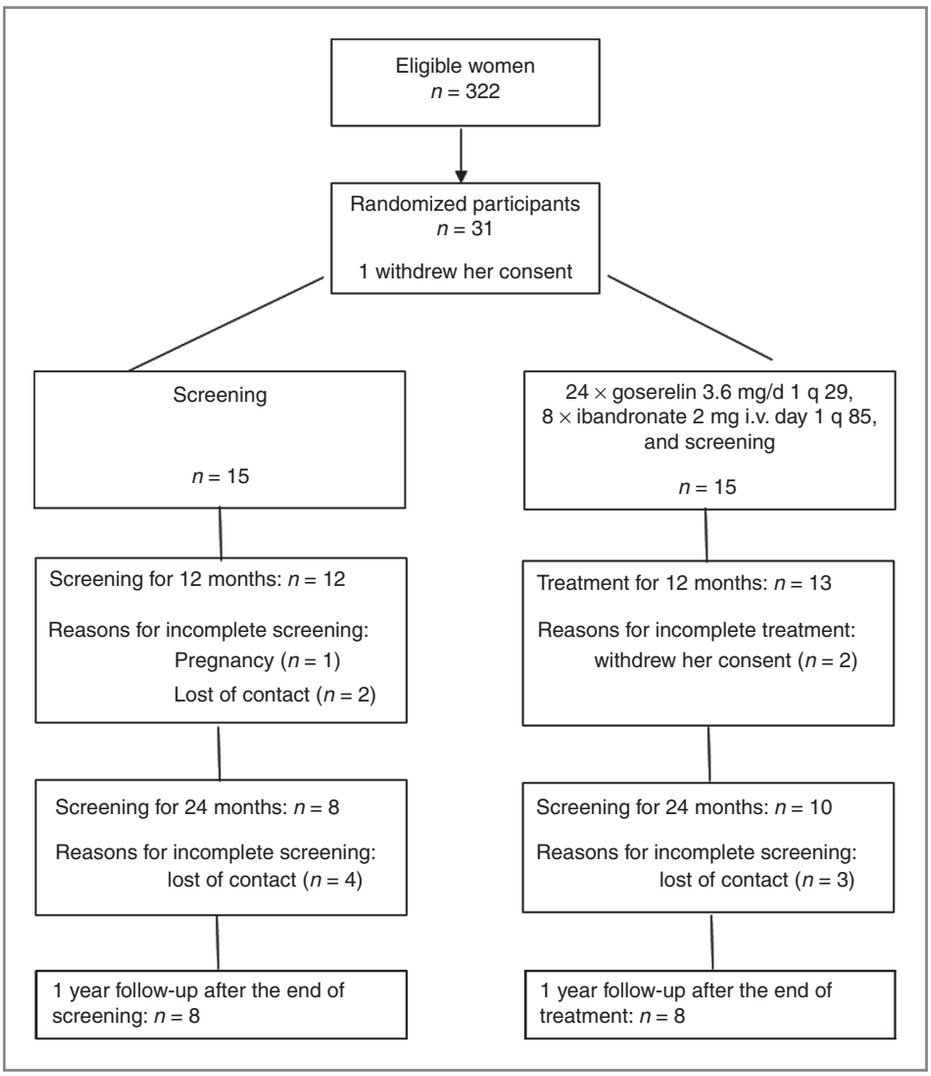

Figure 1. Flow diagram of study participants.

at baseline ($F = 0.31$; $P = 0.587$) and after 12 months ($F = 0.205$; $P = 0.658$). No statistically significant changes in state anxiety were observed during the treatment period with goserelin and ibandronate. Changes in the total score of STAI from baseline to 6 and 12 months are presented in Table 5. There was no significant difference between the 2 arms about the changes.

The cancer worry scale was collected at the baseline. Again, no statistically significant difference between the 2 arms was observed ($t = 1.18$; $P = 0.25$, data not shown).

The FACT-ES. The mean overall symptom score of the FACT-ES changed from 9.1 at baseline to 17.9 at month 12 in the treatment arm and from 9.1 at baseline to 7.8 at month 12 in the screening arm. The difference between the screening and the treatment arm in the change of the total score from baseline to month 12 was −10.01 [95% confidence limits (CL): −17.00 to −3.02; Table 6], indicating a significant difference in favor of the screening arm ($P < 0.05$). A similar difference was observed at month 6 (−11.37; 95% CL: −17.67 to −7.07; $P < 0.05$).

Sexual activity questionnaire. The sexual activity questionnaire was obtained at baseline and after 12 months (Fig. 2).

A statistical evaluation showed no significant differences between the 2 arms after 12 months of study ($F = 1.52$; $P = 0.25$) or between baseline and after 12 months of treatment with goserelin and ibandronate ($F = 2.45$; $P = 0.15$), indicating no impact on sexual activity in the treatment arm.

After 24 months and follow-up evaluation

Similar results were obtained in the remaining 18 participants after 24 months compared with 12 months on the study.

A follow-up evaluation of 16 women, 8 in each arm, was done 1 year after the end of treatment/screening. No breast cancer or loss of bone density was documented. No

Table 4. Number of participants with at least 1 occurrence of toxicity

Toxicity	Arm	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1–4	χ^2 test: *P*
Bone fractures	Treatment					0	0.309
	Screening	1 (6.7%)				1 (6.7%)	
Cardiovascular events	Treatment	4 (26.7%)	1 (6.7%)	1 (6.7%)		6 (40%)	0.231
	Screening	1 (6.7%)	2 (13.3%)			3 (20%)	
Headache	Treatment	1 (6.7%)	5 (33.3%)	6 (40%)	1 (6.7%)	13 (86.7%)	0.020
	Screening	1 (6.7%)	6 (40%)			7 (46.7%)	
Hot flushes	Treatment	1 (6.7%)	7 (46.7%)	4 (26.7%)	2 (13.3%)	14 (93.3%)	0.0001
	Screening	3 (20%)		1 (6.7%)		4 (26.7%)	
Irregular bleeding	Treatment	3 (20%)	2 (13.3%)	2 (13.3%)		7 (46.7%)	0.256
	Screening	3 (20%)	1 (6.7%)			4 (26.7%)	
Nausea	Treatment	2 (13.3%)	5 (33.3%)			7 (46.7%)	0.121
	Screening	1 (6.7%)	2 (13.3%)			3 (20%)	
Vaginal discharge	Treatment	7 (46.7%)	2 (13.3%)	1 (6.7%)	1 (6.7%)	11 (73.3%)	0.003
	Screening	2 (13.3%)	1 (6.7%)			3 (20%)	
Vaginal dryness	Treatment	5 (33.3%)	4 (26.7%)	1 (6.7%)	1 (6.7%)	11 (73.3%)	0.003
	Screening	3 (20%)				3 (20%)	
Vomiting	Treatment	1 (6.7%)				1 (6.7%)	1.000
	Screening		1 (6.7%)			1 (6.7%)	

NOTE: Each toxicity was counted only once by participant but with its highest grade. Total number of participants were 15 in each arm. Duration was 24 months.

statistically significant differences in any adverse events were reported.

Discussion

The GISS trial investigated the acceptance of chemoprevention of breast cancer in premenopausal women with high or moderate risk of breast cancer. Goserelin was applied for temporary suppression of the ovarian function in combination with a bisphosphonate preventing bone loss caused by hypoestrogenemia. Only 10% of eligible women agreed to participate. As observed in other prevention trials, the acceptability of prevention with goserelin was low in young women at increased risk for breast cancer (17, 18). Therefore, because of that low accrual, the GISS trial was closed in December 2003.

Table 5. Comparison of changes in STAI—overall anxiety score[a]—from baseline between study arms

Visit statistics	Goserelin + ibandronate (*N* = 15)		Screening only (*N* = 15)		Difference of change[b]
	Actual	Change	Actual	Change	
Month 0 (baseline)					
n	13		11		
Mean (SD)	36.5 (8.0)		32.1 (3.6)		
95% CL	31.7–41.4		29.7–34.5		
Month 6					
n	8	8	10	7	
Mean (SD)	35.8 (6.3)	1.1 (6.4)	32.5 (9.9)	−0.7 (5.8)	−3.16 (6.09)
95% CL	30.5–41.0	−4.3 to 6.5	25.4–39.6	−6.0 to 4.6	−10.52 to 4.19
Month 12					
n	10	8	8	6	
Mean (SD)	37.0 (10.4)	3.6 (8.3)	36.1 (10.6)	4.3 (11.7)	−0.32 (10.22)
95% CL	29.6–44.4	−3.3 to 10.6	27.3–45.0	−8.0 to 16.6	−13.39 to 12.75

[a]Overall anxiety score was calculated as the sum of 20 single scores between 1 and 4.
[b]Least-squares means of difference between 2 arms and 95% CLs from ANOVA adjusted to baseline.

Table 6. Comparison of changes in FACT-ES—overall symptom score—from baseline between study arms

Visit statistics	Goserelin + ibandronate ($N = 15$)		Screening only ($N = 15$)		Difference of change[a]
	Actual	Change	Actual	Change	
Month 0 (baseline)					
n	13		10		
Mean (SD)	9.1 (7.1)		9.1 (6.3)		
95% CL	4.8–13.4		4.6–13.6		
Month 6					
n	11	9	10	7	
Mean (SD)	13.3 (7.5)	5.8 (7.4)	4.4 (4.3)	−5.4 (6.3)	−11.37 (5.79)
95% CL	8.3–18.3	0.1–11.5	1.3–7.5	−11.2 to 0.4	−17.67 to −5.07
Month 12					
n	9	8	8	5	
Mean (SD)	17.9 (7.8)	8.9 (5.8)	7.8 (3.1)	−1.0 (5.7)	−10.01 (5.50)
95% CL	11.9–23.9	4.1–13.7	5.2–10.3	−8.1 to 6.1	−17.00 to −3.02

Overall anxiety score was calculated as the sum of 20 single scores between 0 and 4.
[a]Least-squares means of difference between 2 arms and 95% CLs from ANOVA adjusted to baseline.

In another randomized prospective trial (RAZOR) applying a preventive treatment with goserelin and raloxifene in premenopausal women at high risk of breast cancer, like in the GISS trial, only 10% of the eligible women (67 of 511) agreed to enter the trial (19). Anticipated side effects might have been overestimated. Shown almost 2 decades ago by Yeomans Kinney and colleagues, anticipated side effects are one of the reasons for women not participating in breast cancer prevention trials. However, older women usually are less likely to participate. (20) The toxicities were tolerable in both trials, and in the present trial, the quality of life in terms of STAI and the sexual activity during the treatment with goserelin and ibandronate were comparable with that in the screening only group. These observations are in concordance with the results of the Zoladex Early Breast Cancer Research Association (ZEBRA) trial comparing the adjuvant use of goserelin with cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy in premenopausal and perimenopausal patients with early breast cancer. Goserelin offered better overall quality of life during the first 6 months of therapy compared with chemotherapy (21). Although prevention drug therapies are well tolerated and do not affect the quality of life, fear of drug side

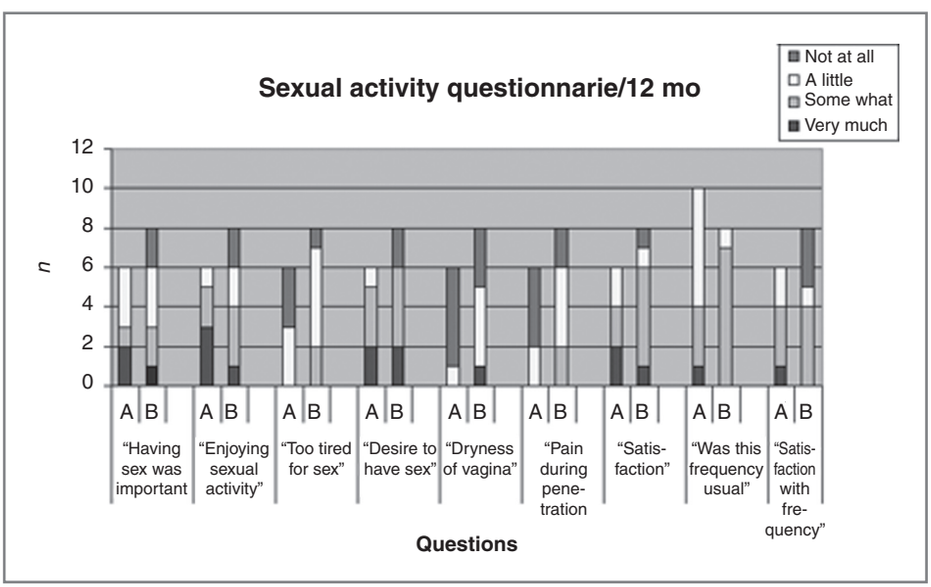

Figure 2. Results of sexual activity questionnaire after 12 months (A: screening only, B: screening plus treatment with goserelin and ibandronate).

effects or medication abuse is still the most common reason for declining treatment (17, 18). Uncertain long-term side effects of chemoprevention with LHRH analogues, such as hypoestrogenemia and menopausal symptoms, are one of the reasons for declining treatment, especially for women desiring pregnancy. As expected, the participants in the treatment arm of the GISS study had a higher total score of FACT-ES, indicating a worse level of endocrine symptoms compared with those in the screening arm. Short-term hormone therapy might be used to treat hypoestrogenemia and to decrease menopausal symptoms in premenopausal women receiving LHRH analogues for prevention. The short-term hormone therapy as add-back treatment was shown to be effective in lowering menopausal symptomas without affecting the prophylactic effect of bilateral ovarectomy on subsequent breast cancer risk in *BRCA* gene mutation carriers (22).

Study design could also impact the acceptability of chemoprevention. For example, short-term trials may increase the acceptability rate and achieve a better compliance than long-term trials (23). In the present trial, the 1-year compliance was good in both the screening and treatment arms ($\geq$80%) whereas after 2 years of treatment, only less than half of the participants still remained in the trial. For trials with 5 years or longer duration, the acceptability of chemoprevention could be as low as 10% (23). In addition, the route of administration also impacts the acceptability of chemoprevention. In the GISS trial, the second most common reason for refusal was "do not like syringe." Oral application of chemoprevention might therefore increase the acceptability rate (23).

Premenopausal women who are at increased risk of developing breast cancer have currently very few medical options for primary prophylaxis. In gene mutation carriers being at high risk of breast cancer, prophylactic ovarectomy is the most commonly carried out procedure for women older than 40 years. The rationale for this surgical intervention in premenopausal women is, beside the reduction of ovarian cancer risk, a decrease in ovarian hormone exposure, which could also be achieved by a reversible medical option. In retrospective studies, Rebbeck and colleagues proved a breast cancer risk reduction of 50% to 53% in women with *BRCA1* and *BRCA2* mutations and an ovarian cancer risk reduction of 96% (24). Two prospective trials confirmed prophylactic bilateral ovarectomy reducing breast cancer and ovarian cancer risk (25, 26). Another surgical procedure applied in women at high risk of developing breast cancer is a bilateral mastectomy, which can reduce breast cancer risk up to 90% in women with a *BRCA1* or *BRCA2* mutation (27). Despite the positive results, these surgical procedures are also not acceptable for many women with a positive family history of breast cancer, although most of them accept genetic testing for risk assessment. Therefore, alternative therapy strategies, for example, chemoprevention, should be explored. Women treated with bisphosphonates have an approximately 30% lower breast cancer risk with an equal effect size for estrogen receptor–negative tumors. (28, 29).

Postmenopausal women have more options as the tamoxifen or raloxifene, a new standard drug in the United States for high-risk breast cancer, which has been proven to be as effective as tamoxifen in reducing the risk of invasive breast cancer in postmenopausal women (30, 31). The third generation of aromatase inhibitors, anastrozole, exemestane, and letrozole, as potential agents for preventing breast cancer in high-risk postmenopausal women are under investigation. First positive results from the MA20 study in 4,560 women at increased risk have been published with exemestane which is lowering the annual incidence of invasive breast cancer by 65% (32).

The GISS study has some strengths and limitations. This is the only trial investigating this concept in premenopausal women. The uptake of preventive measures has been investigated by others but used different methods. Almost all women had a high risk of developing breast cancer according to the definitions in the protocol. However, it might be that the risk benefit analysis is negative in those women with a moderate risk only. Because of low accrual, the study had to be closed prematurely.

In conclusion, the treatment with LHRH analogues, as a nonsurgical option in the prevention of breast cancer, was shown not to be acceptable for most eligible premenopausal women at increased risk. To improve the acceptability and compliance of chemoprevention, better physician counseling and a more practicable recommendation should be provided. A more feasible study design, for example, short-duration trials and oral application of medication, may also help to further elucidate this area.

Disclosure of Potential Conflicts of Interest

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