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Risk factors for negative impacts on sexual activity and function in younger breast cancer survivors

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Abstract

***Objective*: We aim to examine changes in sexual activity and function among younger breast cancer survivors who were sexually active before diagnosis and to investigate risk factors for negative impacts on them.**

***Methods*: An observational cohort study enrolled 304 premenopausal and sexually active women diagnosed with early stage breast cancer. Questionnaires were completed, and sexual activity was measured at two time points: after surgery, to assess sexual activity and function before diagnosis, and then at least 12 months after the completion of chemotherapy or endocrine therapy. For each domain of the Female Sexual Function Index, a score below 3 was classified as indicative of a sexual problem. Each sexual problem was considered to be dysfunctional if it was associated with distress.**

***Results*: The median age at the last survey was 46.0 years (range: 23–57). Of the participants, 35 (11.5%) became sexually inactive after treatment. Among the 269 women who remained sexually active, 31.6% were currently experiencing sexual dysfunction, which was significantly higher compared with the frequency before diagnosis. In the multivariate logistic regression model, chemo-related menopause, thyroid dysfunction, and depression were independent risk factors for sexual inactivity. Chemo-related menopause was a significant risk factor for sexual dysfunction.**

***Conclusions*: Chemo-related menopause was significantly associated with both sexual inactivity and dysfunction after treatment. Thyroid dysfunction and depression were risk factors for sexual inactivity in younger breast cancer survivors.**

Introduction

Breast cancer is the most common cancer in women worldwide, accounting for 23% of total new cancer cases [1]. Although it primarily affects older women, a significant number of breast cancer cases occur among younger women who are still premenopausal; they represent approximately 25% of breast cancer cases in Western countries and much higher proportions in Asian countries [2–4]. Over the past 20 years, earlier diagnoses and advances in treatments have resulted in a marked decline in breast cancer mortality [5], particularly among younger women [6]. As a result, the number of younger breast cancer survivors has increased, and quality of life issues in this population have received more attention.

Sexuality is an important aspect of a woman's life. Although many physical and psychosocial problems related to the treatment of breast cancer dissipate in the year after diagnosis, sexual dysfunction may persist for years after diagnosis with breast cancer [7]. Sexual dysfunction is a common and distressing problem experienced by breast cancer survivors [7,8]. It may be more prevalent among younger breast cancer survivors than their older counterparts because they are more vulnerable to changes in body image after surgery and changes in ovarian function resulting from adjuvant chemotherapy and/or endocrine therapy [9]. Moreover, whereas sexual problems tend to increase with age, the proportion of women distressed about sexual problems decreases with age [10,11].

Previous studies have suggested that breast cancer and its treatment may have a negative influence on sexual activity and function in younger survivors [9,12–18]. Recent studies showed predictors of dysfunction included vaginal pain, poorer body image, and fatigue, and younger survivors reported worse functioning than older survivors relative to depression, fatigue, and spirituality [6,19]. However, most of the studies assessed sexual problems without considering the level of distress. Sexual problems without personal distress may have little clinical importance. Because the current diagnostic guideline from the American Psychiatric Association defines sexual dysfunction as 'more than 6 months, combined with a criterion of "quite often" (occurring in more than at least 75% of sexual encounters) disturbances in sexual desire and in the psychophysiological changes that characterize the sexual response cycle and cause clinically significant distress in the individual' [20], both sexual problems and related personal distress should be considered when assessing sexual

dysfunction. In addition, some studies had a small study population, were cross-sectional, and did not assess sexual activity and function before the cancer diagnosis, which makes the interpretation of the findings problematic [13,16,21,22]. In most of the other research on this subject, the sexual problems were measured only once at a different time period after the surgery. With this approach, it is not possible to determine at which point in time the problems occurred, how long the problems lasted, and whether the problems persisted. In our study, we thoroughly evaluated the patient's progress at least 1 year after the completion of the chemotherapy or hormone treatment for a specific duration of time to account for the consistent finding. Moreover, sexual activity and function can also be affected by various socioeconomic and clinical factors, which have not been fully investigated [9,12,15]. In this study, the factors and distresses affecting the change in sexual activity have been considered comprehensively.

The aim of this study was to examine changes in sexual activity and function among younger breast cancer survivors who were sexually active before diagnosis and to explore risk factors that have negative impacts on them.

Methods

Study population

We conducted an observational study that included a cohort of patients who were referred for a regular gynecologic checkup after breast cancer surgery at Seoul National University Hospital. The protocol was approved by the institutional review board. Subjects were recruited between June 2009 and July 2012. They were selected on the basis of the following inclusion criteria: premenopausal, early stage cancer (ductal carcinoma *in situ* and stage I–IIIA cancer) at diagnosis, no prior history of breast cancer or other malignancies, and having been sexually active before diagnosis. Of them, women who declined to participate in the study, those with a recurrence during the follow-up period, or those who were lost to follow-up were excluded from the final analysis.

Outcome measures

Sexual activity and function were measured at two time points: after surgery (to assess sexual activity and function before diagnosis) and then at least 12 months after the completion of chemotherapy or endocrine therapy using gonadotropin-releasing hormone (GnRH) agonist.

Sexual activity was based on a yes/no response to the question 'Have you had regular sexual intercourse at least once per month?' during the previous 6 months. Women who answered 'no' were considered sexually inactive.

For women who were sexually active, we assessed sexual problems using a validated Korean version of the Female Sexual Function Index [23]. This questionnaire is a 19-item self-reported instrument used for assessing key dimensions of female sexual function over the past 4 weeks with a total of six domains being analyzed: desire (two items), arousal (four items), lubrication (four items), orgasm (three items), satisfaction (three items), and pain (three items). Each item is scored on a scale ranging from either 0–5 or 1–5, with a higher score indicating better performance. The individual domain scores were derived by averaging the responses from the items in each domain. For each domain, a score below 3 was classified as indicative of a sexual problem [24].

Sexuality-related personal distress was measured using a validated Korean version of the Female Sexual Distress Scale [25]. This questionnaire measures a woman's feelings concerning distress about her sex life, assessing guilt, frustration, stress, worry, anger, embarrassment, and unhappiness using a 2-week recall period and a 5-point scale (from 0 = *never* to 4 = *always*) for each of the 20 items. Responses across the items are summed for an overall score, and a score of 20 or higher indicates sexual distress.

Each sexual problem was considered to be a dysfunction if it was associated with distress in accordance with American Psychiatric Association guidelines [20].

Potential risk factors associated with sexual inactivity or sexual dysfunction

We collected data on the potential risk factors associated with sexual inactivity or individual domains of sexual dysfunction from history-taking and medical chart records. These factors included demographic information (age, educational level, and occupational and marital statuses), breast cancer treatment (time since diagnosis and type of breast surgery including reconstruction, chemotherapy, or endocrine therapy), comorbidities, depression, and reproductive history (parity and menopausal status). Premenopause was defined as having regular menstrual cycles within 3 months, regardless of each patient's age. Postmenopause was defined as the cessation of menses for at least 1 year. Chemo-related menopause was defined as the cessation of menses for at least 1 year after chemotherapy. Depression was defined as response of 'yes' to one or more of these questions: (1) Have you been consistently depressed or down, most of the day, nearly every day, for the past 4 weeks? (2) In the past 4 weeks, have you been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time? (3) Are you currently taking medication to treat depression?

Statistical methods

Statistical analyses were performed using SPSS 19.0 for Windows (SPSS, Chicago, IL, USA). The normality of the data for continuous variables was assessed using the Shapiro–Wilk test, which indicated that the data points did not follow normal distributions. Therefore, for the

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continuous variables, comparisons between groups were performed using the Mann–Whitney *U* test. To compare the categorical variables between groups, Fisher's exact test or the chi-square test was performed. Changes in the frequency of sexual dysfunction between the time before diagnosis and after breast cancer treatment were analyzed using McNemar chi-square test.

To identify risk factors that are associated with sexual inactivity or dysfunction, we performed univariate analyses of the potential risk factors, and only variables significant at the 0.05 level were included in the subsequent multivariable logistic regression model. All statistical tests were two-tailed, and statistical significance was defined as $p < 0.05$.

Results

Study population

During the recruitment period, a total of 643 patients were screened for their eligibility. Of them, 300 were excluded because they did not meet inclusion criteria or declined to participate, which left us with 343 patients who were enrolled and assessed for sexual function before the diagnosis. Of them, 39 women were excluded who had recurrence during the follow-up periods ($n = 14$) or were lost to follow-up ($n = 25$). A total of 304 women have fully completed the questionnaire (Figure 1).

Table 1 shows the sociodemographic and clinical characteristics of the study participants. The median age at the last survey was 46.0 years (range: 23–57), and the median time since being diagnosed with breast cancer was 30.0 months (range: 17–40). Most of the women had undergone breast-conserving surgery (BCS), and all of them had received local radiation therapy after surgery. Seventy-one percent of the women had received chemotherapy and/or GnRH agonist therapy (four received both therapies), and 89% were taking endocrine therapy at the time of the last survey. Half of the women became postmenopausal after treatment. No one had a history of prior hysterectomy or bilateral oophorectomy. Other sociodemographic and clinical characteristics are summarized in Table 1.

Sexual inactivity and associated risk factors

Of the participants, 35 (11.5%) became sexually inactive after treatment. The results of the multivariable logistic regression analysis for sexual inactivity are summarized in Table 2, which revealed that women with chemo-related menopause, thyroid dysfunction, or depression were more likely to be sexually inactive ($p < 0.05$). Age, time since diagnosis, educational level, occupational or marital status, parity, type of past breast surgery, past GnRH agonist therapy, current endocrine therapy using tamoxifen or aromatase inhibitors (AIs), comorbidities except for thyroid dysfunction, and any pretreatment sexual dysfunction were not associated with changes in sexual activity.

Sexual dysfunction and associated risk factors

Among the 269 women who remained sexually active, 31.6% were currently having sexual dysfunction in one or more domains, including low desire in 27.5%; low

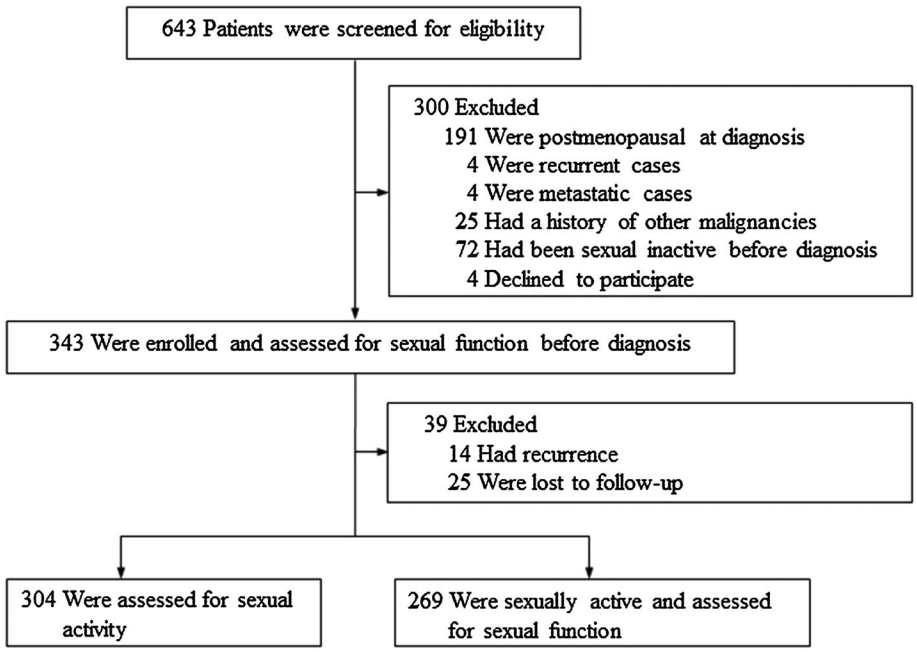

Figure 1. Enrollment and analysis of the study participants.

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Table 1. Characteristic of the study population at last survey ($N = 304$)

Variable	
Age (year), median (IQR)	46.0 (7)
Time since diagnosis (month), median (IQR)	30.0 (8)
Educational level, *n* (%)	
≤high school	152 (50.0)
>high school	152 (50.0)
Occupational status, *n* (%)	
Unemployed	202 (66.4)
Employed	102 (33.6)
Marital status, *n* (%)	
Married	286 (94.1)
Single/widowed/divorced	18 (5.9)
Parity, *n* (%)	
0	23 (7.6)
≥1	281 (92.4)
Type of past breast surgery, *n* (%)	
Conserving surgery	224 (73.7)
Mastectomy with reconstruction	23 (7.6)
Mastectomy without reconstruction	57 (18.8)
Past radiation therapy, *n* (%)	224 (73.7)
Past chemotherapy, *n* (%)	172 (56.6)
Past GnRH agonist therapy, *n* (%)	48 (15.8)
Endocrine therapy, *n* (%)	
None	35 (11.5)
Tamoxifen	252 (82.9)
Aromatase inhibitors	17 (5.6)
Menopausal status, *n* (%)	
Premenopause	150 (49.3)
Postmenopause (not chemo-related)[a]	41 (13.5)
Postmenopause (chemo-related)[a]	113 (37.2)
Comorbidities, *n* (%)	
Hypertension	19 (6.3)
Coronary heart disease or other heart condition	6 (2.0)
Diabetes	5 (1.6)
Asthma	3 (1.0)
Chronic liver disease	6 (2.0)
Chronic renal disease	1 (0.3)
Thyroid dysfunction	15 (4.9)
Arthritis	15 (4.9)
Lymphedema	21 (6.9)
Depression[b], *n* (%)	29 (9.5)

IQR, interquartile range; GnRH, gonadotropin-releasing hormone.
[a]Postmenopause was defined as the cessation of menses for at least 1 year.
[b]Response of 'yes' to one or more of these questions: (1) Have you been consistently depressed or down, most of the day, nearly every day, for the past 4 weeks? (2) In the past 4 weeks, have you been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time? (3) Are you currently taking medication to treat depression?

arousal, 15.2%; low lubrication, 8.6%; low orgasm, 13.8%; low satisfaction, 9.7%; and sexual pain, 11.2%. These frequencies were significantly higher compared with the percentages before diagnosis (Table 3).

Multivariate logistic regression analyses among subjects without sexual dysfunction for individual domains prior to their diagnoses revealed that women with chemo-related menopause were more likely to have sexual dysfunction in all domains ($p < 0.05$). Age, time since diagnosis, educational level, occupational or marital status, parity, type of past breast surgery, past GnRH agonist therapy, current endocrine therapy using tamoxifen or AIs, comorbidities, and depression were not associated with any sexual dysfunction after treatment (Table 4).

Table 2. Risk factors for sexual inactivity (results of multivariable logistic regression analysis)

Variable	OR (95% CI)
Marital status	
Single/widowed/divorced versus Married	3.13 (0.92–10.62)
Past CT/Current menopausal status	
No/Postmenopause	3.00 (0.73–12.26)
Yes/Premenopause	1.45 (0.34–6.17)
Yes/Postmenopause versus No/Premenopause	4.28 (1.37–13.34)*
Thyroid dysfunction	
Yes versus No	3.82 (1.05–13.90)*
Depression	
Yes versus No	2.87 (1.07–7.72)*

OR, odds ratio; CI, confidence intervals; CT, chemotherapy.
*p-value < 0.05.

Discussion

In the present study, we tried to examine the changes in sexual activity and function in younger breast cancer survivors who were sexually active before diagnosis and to explore risk factors that had negative impacts on them. The majority of the women remained sexually active; however, the prevalence of sexual dysfunction significantly increased after cancer treatment. Notably, chemo-related menopause was significantly associated with both sexual inactivity and dysfunction after cancer treatment. Thyroid dysfunction and depression were also associated with sexual inactivity.

Approximately 90% of the patients were consistently sexually active after treatment. This result was in line with the findings of two prospective studies [13,15]. Another short-term follow-up study reported a similar rate of persistent sexual activity (87%) compared with our study [16]. The prevalence of sexual dysfunction after cancer treatment was increased from the pretreatment state, and

Table 3. Percentage of women with sexual dysfunction at prediagnosis and at least 1 year after the completion of chemotherapy and/or endocrine therapy using gonadotropin-releasing hormone agonist

Sexual dysfunction	Before diagnosis	After treatment	*p*-value
Low desire	39 (14.5)	74 (27.5)	<0.05
Low arousal	22 (8.2)	41 (15.2)	<0.05
Low lubrication	6 (2.2)	23 (8.6)	<0.05
Low orgasm	13 (4.8)	37 (13.8)	<0.05
Low satisfaction	11 (4.1)	26 (9.7)	<0.05
Sexual pain	8 (3.0)	30 (11.2)	<0.05
Any	47 (17.5)	85 (31.6)	<0.05

Data are number (%) and analyzed using McNemar chi-square test.

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Table 4. Risk factors for individual sexual dysfunction (results of multivariable logistic regression analyses)

Variable	Low desire	Low arousal	Low lubrication	Low orgasm	Low satisfaction	Sexual pain
Age, year	1.05 (0.96–1.14)	1.05 (0.95–1.16)	NA	1.04 (0.94–1.15)	1.11 (0.98–1.26)	1.05 (0.94–1.18)
Current endocrine therapy						
Tamoxifen	NA	NA	NA	NA	NA	0.78 (0.19–3.10)
Aromatase inhibitors versus None	NA	NA	NA	NA	NA	1.95 (0.34–11.03)
Past CT/Current menopausal status						
No/Amenorrhea	0.93 (0.28–3.06)	2.86 (0.68–11.98)	0.81 (0.08–8.10)	1.63 (0.33–8.13)	1.03 (0.16–6.85)	0.52 (0.05–5.15)
Yes/Premenopause	0.48 (0.12–1.93)	0.96 (0.16–5.82)	0.52 (0.05–5.15)	0.45 (0.05–4.35)	0.83 (0.08–8.84)	0.42 (0.04–4.26)
Yes/Amenorrhea versus No/Premenopause	2.81 (1.26–6.27)*	4.81 (1.53–15.18)*	4.68 (1.27–17.23)*	5.46 (1.75–16.99)*	4.53 (1.24–16.55)*	3.52 (1.05–11.82)*
Diabetes						
Yes versus No	NA	NA	3.94 (0.60–26.13)	NA	NA	4.84 (0.67–34.84)
Lymphedema						
Yes versus No	NA	NA	NA	NA	NA	2.78 (0.79–9.80)

CT, chemotherapy; NA, not applied.
Data are odds ratio (95% confidence intervals) and analyzed among subjects without sexual dysfunction for individual domain before diagnosis with breast cancer.
*p-value < 0.05.

all domains had statistically significant changes. However, compared with other studies, the prevalence of sexual dysfunction (31.6%) was low in this study. This may be explained by the difference in the definition of sexual dysfunction. A recent large cross-sectional survey reported that the prevalence of distressing sexual problems was lower than the prevalence of sexual problems [26]. Unlike this study, most of the previous studies did not consider personal distress; the prevalence was higher than our data. The exclusion of advanced stage and recurrent breast cancer may also account for lower rates of sexual dysfunction in this study.

We hypothesized that various factors, including surgery type, radiation, chemotherapy, and endocrine therapy, will affect patients' sexual activity and function. However, chemo-related menopause and thyroid dysfunction affected sexual activity, and chemo-related menopause was the only independent risk factor for sexual dysfunction. We found the negative correlation between depression and sexual activity. However, given the cross-sectional sentences of the data, this does not imply that depression is causing the change in sexual activity.

Several studies showed that detrimental effects on sexuality have been attributed to chemotherapy [15,27,28]. Ganz *et al.* [12] found that sexual function was most impaired for women who stop menstruating after chemotherapy. However, other studies that found a long-term effect of chemotherapy had only studied premenopausal women and had not evaluated sexual activity [13,29]. The long-term impact of chemotherapy on sexual function may be related to its impact on ovarian function. Chemotherapy disrupts ovarian hormone production, lowering circulating levels of estrogens. Levels of androgens, which presumably promote sexual desire, also decline. These effects may be prolonged, creating continued sexual problems. Therefore, women whose ovarian function is severely affected by chemotherapy may show long-term effects.

A prior prospective study demonstrated that GnRH agonist, among endocrine therapy agents, increased sexual dysfunction during treatment, similar to the effect of chemotherapy. However, all endocrine treatment effects were reversible upon cessation of treatment [13]. Consistent results were shown in this study. Tamoxifen and AIs also had no significant impact on sexual activity and function. Tamoxifen exerts weak estrogenic effects on vaginal epithelium and increases the bioavailable fraction of androgens, which may explain these outcomes. Endocrine therapy with AIs has been associated with increased vaginal dryness and dyspareunia [30]. However, the proportion of AIs-treated patients was low, and AIs did not have significant negative effects on sexual activity and function.

In our analyses, the nature of the surgeries performed had no significant bearing on sexual dysfunction, but previous research on the sexual ramifications of breast cancer surgery has been controversial. According to some studies, the highest rates of satisfaction, in terms of physical appearance and sexual life, are achieved with BCS [31,32]. Still, there are other studies comparing BCS and total mastectomy that indicate no difference in quality of life [33,34]. Body image is better in women who received BCS, as opposed to a mastectomy, but this factor is the only one from which sexuality is impacted [35]. Giving the patient an active role in the choice of surgery, rather than the extent of the surgery itself, seems to be a major determinant of satisfaction with self-body image [36]. Patients who underwent breast reconstruction may experience more sexual dysfunction than formerly appreciated in the literature, stemming perhaps from expectations that are unmet when breast-sparing surgery is medically prohibited.

In addition to cancer treatment, sociodemographic factors and medical comorbidities were investigated to identify risk factors for sexual inactivity and dysfunction. Education level and occupational status were not

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significantly associated with sexual dysfunction, which was consistent with previous studies. Mood disorders, such as anxiety and depression, are highly prevalent in breast cancer patients. These disorders correlate with sexual dysfunction, especially in the domain of low desire [37]. In this study, depression and thyroid dysfunction had negative effects not on sexual dysfunction, but rather on sexual activity. A recent study reported that women with thyroid disease present with a higher prevalence of sexual dysfunction than control subjects [38,39]. Therefore, negative effects on sexual function may affect sexual activity. However, the subjects of these studies were non-cancer patients, and some were men. Therefore, it is necessary to conduct studies with higher levels of evidence to clarify the effects of thyroid dysfunction on sexual dysfunction in cancer patients.

The major advantages of our study are the relatively large sample size, the prospective design, the use of validated instruments to measure sexual problems and sexual distress, the application of DSM-V criteria for classifying sexual problems as sexual dysfunction, and the consideration of various sociodemographic and clinical factors in addition to cancer treatment. We also checked for a change in menstruation status after receiving chemotherapy.

The limitations of this study are that the results are based on retrospective recollections of sexual activity and functioning pretreatment, which can be biased either positively or negatively by each woman's cancer experience.

Second, relationships with sexual partners, and perceived partner dysfunction were not explored. A previous study reported that sexual desire, arousal, and orgasm in a woman can be influenced by the quality of her relationship and her partner's sexual function and overall health [40]. Therefore, further study on these factors is needed.

Third, the results of our study are limited to sexually active women. Because the Female Sexual Function Index is an instrument designed for and validated on sexually active women, it is difficult to know the level of sexual function among women who had sexual intercourse less than once per month. To overcome this problem, we also evaluated changes in sexual activity and related risk factors together.

Fourth, not all patients visit the gynecologic clinic after breast cancer surgery, even though almost all who are planning to receive adjuvant endocrine therapy are referred for a regular gynecological checkup. This is one of the limitations because not all patients are included in this study.

Finally, this study's participants are Asian and premenopausal women. Therefore, further studies are needed for other races and for postmenopausal women.

In conclusion, most of the younger breast cancer survivors were sexually active after treatment. Chemo-related menopause was significantly associated with both sexual inactivity and dysfunction after treatment. Thyroid dysfunction and depression were risk factors for sexual inactivity in younger breast cancer survivors.

Conflict of interest

The authors have no conflicts of interest to declare.

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