HHS Public Access

Author manuscript

Breast Cancer Res Treat. Author manuscript; available in PMC 2024 July 01.

Published in final edited form as:

Breast Cancer Res Treat. 2023 July ; 200(1): 103–113. doi:10.1007/s10549-023-06953-9.

Breast Cancer Survivorship and Sexual Dysfunction: a Population-based Cohort Study

Chun-Pin Chang, PHD MPH[1,2,&], **Tiffany F. Ho, MD MPH**[1,&], **John Snyder, MS**[3], **Mark Dodson, MD**[3,4], **Vikrant Deshmukh, PhD**[5], **Michael Newman, MS**[5], **Ankita Date, MS**[6], **N. Lynn Henry, MD PhD**[7], **Mia Hashibe, PhD**[1,2]

[1]Division of Public Health, Department of Family & Preventive Medicine, University of Utah School of Medicine, Salt Lake City, Utah, USA

[2]Huntsman Cancer Institute, Salt Lake City, Utah, USA

[3]Intermountain Healthcare, Salt Lake City, Utah, USA

[4]Department of Obstetrics and Gynecology, University of Utah School of Medicine, Salt Lake City, Utah, USA

[5]University of Utah Health Sciences Center, Salt Lake City, Utah, USA

[6]Pedigree and Population Resource, Population Sciences, Huntsman Cancer Institute, Salt Lake City, Utah, USA

[7]Division of Hematology/Oncology, University of Michigan Medical School, Ann Arbor, Michigan, USA

Abstract

Background: Breast cancer is the most common non-skin cancer in women and an increasing number of people are living as breast cancer survivors. While the prognosis of breast cancer continues to improve, the rates of sexual dysfunction and the risk related to cancer treatments have not been well characterized in a population-based study.

Methods: We identified a cohort of 19,709 breast cancer survivors diagnosed between 1997–2017 from the Utah Cancer Registry, and 93,389 cancer-free women who were matched by age and birth state from the Utah Population Database. Sexual dysfunction diagnoses were identified through ICD-9 and ICD-10 codes from electronic medical records and statewide healthcare facilities data. Cox proportional hazard models were used to estimate hazard ratios for risk of sexual dysfunction.

Corresponding author: Mia Hashibe, Ph.D., Division of Public Health, Department of Family and Preventive Medicine, Huntsman Cancer Institute, 2000 Circle of Hope, Salt Lake City, UT, 84112, mia.hashibe@utah.edu.
&Chun-Pin Chang and Tiffany Ho contributed equally to this work.

Author contributions: Conceptualization: C.C., T.H.. Formal Analysis: C.C.. Funding Acquisition: M.H.. Investigation: C.C., T.H., M.H.. Methodology: C.C., T.H., M.H.. Writing (original draft): C.C., T.H., M.H.. Writing (review and editing): C.C., T.H., J.S., M.D., V.D., M.N., A.D., N.L.H., M.H.

Disclosures: The authors have no conflicts of interest to disclose.

Conflict of Interest: The authors declare that they have no conflict of interest.

Results: Breast cancer survivors were at higher risk of sexual dysfunction diagnosis (9.1% versus 6.9%, HR 1.60 95%CI 1.51–1.70) compared to the general population. This risk increased 2.05-fold within 1 to 5 years after cancer diagnosis (95%CI 1.89–2.22) and 3.05-fold in individuals diagnosed with cancer at <50 years of age (95%CI 2.65–3.51). Cancer treatments including endocrine therapy, chemotherapy and radiation therapy were associated with an increased risk of sexual dysfunction among breast cancer survivors.

Conclusions: Risk of sexual dysfunction in breast cancer survivors is higher than in the general population, but may be underdiagnosed in the clinical setting. Health care professionals should be encouraged to address the topic of sexual health early on in the treatment of breast cancer, and routinely screen patients for symptoms of sexual dysfunction.

Precis:

Compared to women in the general population, breast cancer survivors are at higher risk of having sexual dysfunction but are likely underdiagnosed. Health care providers may need to routinely inquire with cancer survivors about sexual health.

Keywords

breast cancer; cancer survivorship; sexual dysfunction; sexual health; population-based

Introduction

Breast cancer remains the most common non-skin cancer in women, representing 30% of all reported cancer cases in women within the United States[1]. Although the incidence of breast continues to increase, female breast cancer death rates have declined due to earlier detection and treatment [1, 2]. Breast cancer survivors comprise the largest proportion of cancer survivors in the United States, with a 5-year survival rate of approximately 90% [2, 3]. Despite the data showing that most survivors have a good prognosis, current treatments can result in problems that affect quality of life. One commonly reported concern by breast cancer survivors is sexual health [4–7].

Sexual functioning is an important element of quality of life. Many women experience sexual problems as a result of a breast cancer diagnosis and its treatment. The reported prevalence of sexual dysfunction varies from 30% to 100%, including symptoms such as low sexual desire, dyspareunia (pain with intercourse), vaginal dryness, and/or anorgasmia [4, 7–13]. This variability may be attributed to differences in study methods such as how sexual dysfunction is defined and reported. Multiple models of the female sexual response have been proposed, most of which include the psychological (desire, intimacy) and physical (arousal, orgasm) components of sexual health [14, 15]. The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5) identifies three female dysfunctions which includes female sexual interest/arousal disorder (formerly female hypoactive desire disorder and arousal disorder), genito-pelvic pain/ penetration disorder (formerly separate dyspareunia and vaginismus) and female orgasmic disorder [16]. These are typically used in the clinical setting for diagnosis.

Female sexual health concerns may present along the continuum of an individual's breast cancer diagnosis – from even before their diagnosis, arise around the time of diagnosis, or result as a consequence of treatment. Despite being such a common issue, the topic of sexual health in cancer survivors is reportedly under addressed in the clinical setting. It is estimated fewer than 25% of those with sexual problems get help from a health professional [7, 17–19]. Part of this is explained by an assumption by clinicians that patients will initiate the discussion rather than needing to be asked directly [20]. Patients reported fear of dismissal, perceived discomfort on the part of the physicians, and concern for lack of treatment options as reasons not to discuss sexual health issues [21].

Several smaller-scale studies have investigated the *prevalence* of sexual dysfunction amongst breast cancer survivors in the United States [4, 6, 22–24]. However, there has not been a population-based study investigating the *incidence* of sexual dysfunction diagnosis in women with breast cancer within the United States. The aim of our study was to estimate the risk of sexual dysfunction diagnosis in breast cancer survivors compared to a general population cohort and to identify risk factors for sexual dysfunction.

Methods

The Institutional Review Board at the University of Utah and the Resource for Genetic and Epidemiologic Research and the oversight committee for the Utah Population Database approved the current study.

Data source

We used the Utah Population Database (UPDB) to conduct the population-based cohort study. UPDB links data from the Utah Cancer Registry, electronic medical records (EMRs), statewide healthcare facility data, driver licenses, voter registration, family history records, residential histories, and birth and death certificates for the population of the state of Utah. The Utah Cancer Registry maintains the records of patients in Utah with cancer beginning in 1966 and has been part of the National Cancer Institute's (NCI) Surveillance Epidemiology and End Results (SEER) program since 1973. The hospital EMR source was from the two major healthcare systems in Utah: the University of Utah and Intermountain Healthcare hospitals [25, 26]. The statewide healthcare facility data for ambulatory surgery and emergency department encounters date back to 1996, and the encounter records for inpatient discharge date back to 1992, agnostic to payer source (uninsured, private insurance, Medicaid, Medicare, and Public Employee Health Plans (PEHPs)) [27].

Study population

Women 18 years of age or older diagnosed with a first primary invasive breast cancer from January 1997 to December 2017 were identified in the Utah Cancer Registry. Breast cancer diagnosis was classified according to the International Classification of Diseases for Oncology, Version 3 (ICD-O-3 code: C50). In order to calculate baseline comorbidity scores, we restricted the year of cancer diagnosis since 1997, to ensure the availability of high quality EMR data. Given that the goal of this investigation was to evaluate the impact

of cancer treatment on long-term sexual dysfunction, we excluded women who died within a year of cancer diagnosis (n=1,060).

A population-based comparison group was selected from the UPDB. Breast cancer survivors were matched with up to five cancer-free women from the general population by age (± 2 years) and birth state (Utah/non-Utah). We matched for birth state because individuals who were born in Utah may have more detailed health records over their lifespan than Utah residents who grew up in other states. The baseline date was defined as the date of cancer diagnosis for breast cancer survivors. For women from the general population, the baseline date was defined as the date of cancer diagnosis for the cancer survivor that the individual was matched to. Similar to the criteria for breast cancer survivors, we excluded women who had a follow-up period of one year or less in the comparison group (n=2,602).

Study variables

Information on the date of cancer diagnosis, tumor characteristics, and first-course cancer treatment for the breast cancer survivors was obtained from the Utah Cancer Registry. Information about comorbidities and sexual function symptoms was obtained from the Utah statewide healthcare facility data as well as EMR data. We used ICD-9 and ICD-10 diagnosis codes to identify sexual dysfunction including dyspareunia, vaginal dryness/ atrophic vaginitis, decreased libido, lack of arousal (female sexual arousal disorder), lack of orgasm (female orgasmic disorder), and other sexual dysfunction (Supplementary Table 1 shows the ICD codes used).

Statistical analysis

Demographic characteristics between breast cancer survivors and cancer-free women were compared, along with the clinical characteristics of the breast cancer survivors. Women who did not develop sexual dysfunction were censored at death or last known residence date in Utah, whichever came first. We evaluated the risk of sexual dysfunction in three time periods: overall (>1 year), >1 to 5 years, and >5 years after cancer diagnosis or the baseline date. Women diagnosed with the outcome of interest before the study period were considered to have a prevalent disease and were excluded from the analyses for that outcome. Cox proportional hazards models stratified on matched pairs were used to estimate hazard ratios (HRs) and 95% confident intervals (CIs) for the risk of incident sexual dysfunction with adjustment for potential confounders, including race/ethnicity, baseline body mass index (BMI), baseline Charlson Comorbidity Index (CCI). Potential confounding factors were chosen a priori based on the three properties of confounders determined by a causal model, a directed acyclic graph (DAG) [28]. The baseline CCI was calculated using data prior to the baseline date [29]. The proportional hazards assumption was tested for each Cox proportional hazards model by including interactions between the predictors and time in the model. For models where the assumption was violated, we compared the estimates from the flexible parametric survival model with restricted cubic splines [30, 31] and the Cox model. The estimate from the flexible model was used if the inference was different between two models. Height and weight for women were obtained from the Utah driver license data at least one year prior to baseline and were used to calculate baseline BMI. Approximately 20.2% of the breast cancer survivors and 17.7% of the general population had missing

information for baseline BMI. We imputed the BMI value using a linear regression model with cancer diagnosis, baseline CCI, race, and age at baseline as covariates. Hazard ratios with and without the imputed BMI were compared to assure that the inferences did not change. Analyses were performed using SAS software (version 9.4, SAS Institute).

Results

The final cohort included 19,709 breast cancer survivors and 93,389 women from the general population. A higher portion of breast cancer survivors identified as Asian, Native Hawaiian/Pacific Islander or multiple races while the general population had a higher proportion of individuals who identified as either Native American or unknown ($p<0.001$; Table 1). Amongst breast cancer survivors, 61.6% were diagnosed with localized cancer (Table 2). Ductal carcinoma was the most common type of breast cancer identified on histology (73.4%). Of the patients diagnosed with breast cancer, 96.5% underwent surgery, 56.2% received radiotherapy, and 42.6% received chemotherapy. Breast cancer survivors had a slightly lower prevalence of decreased libido compared to the general population ($p=0.006$); however, there was no difference in the prevalence of other sexual function symptoms (Supplemental Table 2).

Approximately 9.1% of breast cancer survivors reported sexual function symptoms at >1 year after cancer diagnosis compared to 6.9% of the general population (Table 3). Compared to the general population, breast cancer survivors had a 1.60-fold increased risk of all time sexual function symptoms (95% CI 1.51–1.70). This increased risk of sexual function symptoms was observed within >1 to 5 years after cancer diagnosis (HR 2.05, 95% CI 1.89–2.22) as well as > 5 years after cancer diagnosis (HR 1.24, 95%CI 1.13–1.35). Within the overall follow up period, breast cancer survivors had higher risks of vaginal dryness/atrophic vaginitis (7.0% vs 5.4%; HR 1.51, 95% CI 1.41–1.61), vaginal complication (3.0% vs 1.8%; HR 2.04, 95% CI 1.84–2.26), dyspareunia (0.8% vs 0.6%; HR 1.79, 95% CI 1.49–2.15) and decreased libido (0.4% vs 0.3%; HR 1.48, 95%CI 1.14–1.92) compared to the general population. The risks of each of these sexual function symptoms varied between >1 to 5 years after cancer diagnosis and >5 years after cancer diagnosis. The sexual function symptoms that cancer survivors persistently were at higher risk of >5 years after cancer diagnosis included vaginal dryness/atrophic vaginitis (HR 1.22, 95%CI 1.10–1.34) and vaginal complication (HR 1.47, 95%CI 1.26–1.72).

The incidence of sexual function symptoms was further stratified by age group for breast cancer survivors between >1 to 5 years after diagnosis and the general population (Table 4). The risk of sexual function symptoms was higher in breast cancer survivors compared to the general population across all age groups, and the highest risk was seen in individuals less than 50 years old (HR 3.05, 95%CI 2.65–3.51). For individuals less than 50 years old, they had higher rates of dyspareunia (HR 2.89, 95%CI 2.08–4.03), vaginal dryness (HR 2.81, 95%CI 2.37–3.33), vaginal complications (HR 3.67, 95%CI 2.95–4.56), and decreased libido (HR 3.09, 95%CI 2.00–4.77) compared to the general population. Breast cancer survivors between the ages of 50 and 65 years were also at higher risk for dyspareunia (HR 1.95, 95%CI 1.31–2.91), vaginal dryness (HR 1.85, 95%CI 1.60–2.14) and vaginal complication (HR 2.89, 95%CI 2.30–3.64) and decreased libido (HR 1.96, 95%CI 1.09–

3.53). For breast cancer survivors over the age of 65, they were at higher risk of having vaginal dryness (HR 1.34, 95%CI 1.13–1.59) and vaginal complication (HR 1.51, 95%CI 1.11–2.08).

Breast cancer survivors' risk of sexual function symptoms varied based on the type of treatment they received (Table 5). ER positive cancers were associated with a 1.29-fold higher risk of sexual function symptoms (95% CI 1.12–1.48). Breast cancer survivors who received endocrine therapy had a 1.46-fold higher risk of sexual function symptoms > 1 year after diagnosis (95% CI 1.32–1.62). Breast cancer survivors who received radiation therapy (HR 1.17, 95% CI 1.06–1.30) or chemotherapy (HR 1.16, 95% CI 1.03–1.30) also had a higher risk of sexual function symptoms. Among breast cancer survivors who had surgical treatment, there was no statistically significant difference in the risk of sexual function symptoms among breast cancer survivors who underwent breast-conserving surgery, total mastectomy, and radical mastectomy (data not shown). Breast cancer survivors diagnosed at >=50 years of age had a 1.69-fold higher risk of sexual function symptoms (95% CI 1.52–1.88). Higher baseline body mass index decreased risk of sexual function symptoms. For breast cancer survivors categorized as overweight (BMI 25–29.9), the risk of sexual function symptoms was 0.85 (95%CI 0.75–0.95) and for women who were obese (BMI >= 30), the risk of symptoms was 0.77 (95%CI 0.67–0.89). Risk factors including cancer stage, ethnicity, and rural residence at baseline were not associated with the risk of sexual function symptoms.

Discussion

We examined sexual dysfunction diagnosis among breast cancer survivors in a large population-based cohort. Compared to the general population, we observed increased risks of sexual function symptoms including dyspareunia, vaginal dryness, vaginal complications, and decreased libido among breast cancer survivors. This difference was most prominent within the first five years of cancer diagnosis, particularly in breast cancer survivors who were <50 years old at the time of breast cancer diagnosis. Risk factors for sexual dysfunction affected breast cancer survivors who received radiation, chemotherapy, and endocrine therapy. Higher baseline body mass index was associated with lower risk of sexual function symptoms among breast cancer survivors.

Most women with breast cancer will undergo some form of surgery coupled with radiation therapy, chemotherapy, endocrine therapy and/or targeted therapy to reduce the risk of recurrence. In our study, more than 95% of breast cancer survivors received surgical treatment, and patients who did not receive surgery were more likely to have metastatic disease. Prior studies have shown women who had a mastectomy reported higher rates of sexual dysfunction symptoms post-operatively compared to women who underwent breast-conserving surgery [10, 23, 32]. However, in our study there was no statistically significant difference in the risks of sexual function symptoms among the various types of surgeries (i.e. breast-conserving surgery, total mastectomy, radical mastectomy). This is supportive of other studies which have not shown a significant difference [4, 17, 18].

Prior studies examining the effects of chemotherapy on sexual dysfunction reported mixed results on the risk of sexual dysfunction, as most of them compared outcomes with other cancer treatment modalities [4–6, 9, 23, 33]. Our study compares the risk of sexual dysfunction amongst breast cancer survivors based on treatment received. Breast cancer survivors treated with chemotherapy had a 1.16-fold risk of sexual dysfunction compared to individuals who did not receive chemotherapy. An important side effect of chemotherapy is the induction of premature menopause in younger women, which has been shown to contribute to poorer sexual functioning beyond the decline normally associated with aging [6].

Furthermore, our study shows that breast cancer survivors had an increased risk of sexual dysfunction diagnosis by 1.46-fold if they received endocrine therapy and a 1.17-fold risk if they had radiation. The primary aim of endocrine therapy is to induce estrogen deprivation at the estrogen receptor level (tamoxifen) or to inhibit estrogen biosynthesis (aromatase inhibitors). Although our study groups these treatments together, prior studies have concluded the sexual side effects do differ. Compared to breast cancer survivors not on endocrine therapy, breast cancer patients treated with aromatase inhibitors have significantly higher rates of vaginal dryness, dyspareunia, loss of sexual interest, and general dissatisfaction with their sexual life [6, 9, 24, 34]. For tamoxifen-treated breast cancer survivors, some previous studies reported higher rates of vaginal dryness and dyspareunia while many other studies found no significant difference in sexual function. For radiation therapy, prior studies have shown that breast cancer survivors who underwent radiotherapy had lower sexual well-being scores due to both physical impacts (mobility, deformity) and psychosocial effects (body image) [5, 35].

We observed that higher baseline BMI was associated with a lower risk of sexual dysfunction. One possible explanation is that higher BMI may be protective against menopausal symptoms due to higher estrone production in adipose tissue which could supplant declining estradiol levels in later reproductive years [36, 37]. There is concern that people with higher BMI have worse survival outcomes with cancer treatments such as chemotherapy, but results have been mixed [38, 39]. Further studies will be needed to risk stratify breast cancer survivors by age, BMI and cancer treatment to confirm if BMI is indeed protective for sexual dysfunction and therapy-induced menopause.

Despite the prevalence of sexual health toxicities in women treated for breast cancer, estimates are that less than half will seek and/or receive medical evaluation [5]. The largest study to date examining sexual dysfunction after breast cancer was performed in Australia, in which 70% of the 1,011 women in a prospective cohort study self-reported sexual function concerns [7]. In our study, only 9.1% of breast cancer survivors were diagnosed with sexual dysfunction. The dramatic difference in percentages between these two studies is not likely to be due to country variation. In prior studies, the most common approaches to assess sexual dysfunction included interview questions, study-specific self-report instruments and standardized questionnaires [4, 6, 7, 9, 24, 34, 40]. Our study relied on ICD-9 and ICD-10 codes which require clinical providers to diagnose breast cancer survivors with symptoms of sexual dysfunction and code the diagnosis in the EMR for

billing. The difference in percentages of sexual dysfunction reflects potential underdiagnosis of such issues in a clinical setting.

The American Society of Clinical Oncology recommends that a member of the health care team should initiate a discussion regarding sexual health and dysfunction resulting from cancer or its treatment [41]. Barriers to discussing sexual health issues with a health care professional (primary care, oncology, surgeon, Ob/GYN etc) are multi-factorial. Krychman et al. encourage all health care providers to inquire about patients' sexual history as part of their routine assessments in order to promote an open conversation about it at any appointment, but time is often another cited barrier [17]. Patients may be unwilling to discuss personal and sensitive topics and the providers may not have the training, awareness or comfort level to engage in sexual health discussions [2, 5, 21, 42]. Although not all health professionals may know how to develop treatment plans for sexual dysfunction, they should be familiar with how to diagnose this under addressed condition and be familiar with existing resources and guidelines and/or provide appropriate referrals [5, 17, 18, 20, 41, 43, 44]. In medical school, sexual education has focused more on contraception counseling and prevention of sexually transmitted diseases rather than sexual dysfunction [45, 46]. There has been growing curricula to standardize how to obtain comprehensive sexual histories including sexual wellness[47, 48]. Medical students and physicians who perceived they had adequate training in sexual health during medical school was associated with feeling comfortable addressing patients' sexuality across the lifespan[46, 48]. Similar trainings across health care disciplines are needed given the multi-disciplinary team breast cancer survivors interact with.

A limitation of this study is the generalizability. Our study cohort was less diverse in race and ethnicity. However, the Hispanic population is growing rapidly in Utah. Another limitation is our study was that we were not able to stratify breast cancer survivors based on their menopausal status, although we stratified on age as a proxy. Issues that may be related to cancer treatment often intersect with normal sexual and reproductive health changes that occur as one age such as menopause. Furthermore, the percentage of patients who received endocrine therapy was underestimated and did not specify if they received aromatase inhibitors or tamoxifen. We used ER positive as a surrogate for endocrine therapy and cancer diagnosis age as a proxy for the use of tamoxifen or aromatase inhibitors in the analysis. Cancer patients may be more likely to visit clinics for the follow-up care during the first 5 years of breast cancer diagnosis compared to women from the general population, leading to increased surveillance. However, the associations we observed >5 years after cancer diagnosis should be less affected by increased surveillance.

Sexual dysfunction will continue to be an important health concern for this unique population. One major challenge existing in clinical practice is the barrier to communication of such sensitive issues between the health care provider and patient, thus the under-diagnosis of this important health condition. Further research is needed to develop interventions to standardize or integrate the conversation about sexual health in routine clinical appointments. The evaluation of sexual health can be aided by the use of a validated questionnaire. The American Society of Clinical Oncology recommends screening tools such as those from the National Comprehensive Cancer Network [49] and Patient-Reports

Outcomes Measurement Information System (PROMIS-1) item screener [50]. Gender-specific tools include the female sexual function index (FSFI) [43] or Arizona Sexual Experience Scale (ASEX) [51], both of which have been validated in cancer survivors.

In conclusion, we observed that breast cancer survivors experienced increased risks of sexual dysfunction symptoms such as dyspareunia, vaginal dryness, vaginal complications, and decreased libido and these women were likely underdiagnosed. Health care professionals should be encouraged to address the topic of sexual health throughout the treatment of breast cancer, and routinely screen patients for symptoms of sexual dysfunction. The right moment to approach sexuality is a great challenge in daily practice and should be prioritized because the identification of specific needs for cancer survivors can improve their quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding.

This work was supported by grants from the NIH (R21 CA185811, R03 CA159357, M.Hashibe, PI), the Huntsman Cancer Institute, and the Cancer Control and Population Sciences Program (HCI Cancer Center Support Grant P30CA042014). This research was supported by the Utah Cancer Registry, which is funded by the National Cancer Institute's SEER Program, Contract No. HHSN261201800016I, the US Center for Disease Control and Prevention's National Program of Cancer Registries, Cooperative Agreement No. NU58DP0063200, with additional support from the University of Utah and Huntsman Cancer Foundation. Research was supported by the NCRR grant, "Sharing Statewide Health Data for Genetic Research" (R01 RR021746, G. Mineau, PI) with additional support from the Utah Department of Health and Human Services and the University of Utah. Partial support for all datasets within the Utah Population Database is provided by the University of Utah, Huntsman Cancer Institute and the Huntsman Cancer Institute Cancer Center Support grant, P30 CA2014 from the National Cancer Institute, and Intermountain Healthcare. We thank the Utah Clinical and Translational Science Institute (CTSI) (funded by NIH Clinical and Translational Science Awards), the Pedigree and Population Resource, University of Utah Information Technology Services and Biomedical Informatics Core for establishing the Master Subject Index between the Utah Population Database and the University of Utah Health Sciences Center. The computational resources used were partially funded by the NIH Shared Instrumentation Grant 1S10OD021644-01A1.

Role of the funder:

The funders had no role in study design; data collection, analysis, and interpretation; manuscript written; or the decision to submit the manuscript for publication.

Data availability:

The data that support the findings of this study are available upon request with appropriate approval from the Resource for Genetic and Epidemiologic Research (RGE) and IRB approval. The data are not publicly available due to privacy or ethical restrictions.

Reference

1. American Cancer Society (2021) Breast Cancer Facts & Figures 2019–2020 In:American Cancer Society, Inc., Atlanta
2. Centers for Disease Control and Prevention (2021) United States Cancer Statistics Breast Cancer Stat Bite In:Centers for Disease Control and Prevention, US Department of Health and Human Services, Atlanta, GA

3. Cancer US Statistics Working Group (2021) U.S. Cancer Statistics Data Visualizations Tool, based on 2020 submission data (1999–2018. In:U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute
4. Barni S, Mondin R (1997) Sexual dysfunction in treated breast cancer patients. Ann Oncol 8:149–153. doi: 10.1023/a:1008298615272 [PubMed: 9093723]
5. Boswell EN, Dizon DS (2015) Breast cancer and sexual function. Transl Androl Urol 4:160–168. doi: 10.3978/j.issn.2223-4683.2014.12.04 [PubMed: 26816822]
6. Ganz PA, Rowland JH, Desmond K, Meyerowitz BE, Wyatt GE (1998) Life after breast cancer: understanding women's health-related quality of life and sexual functioning. J Clin Oncol 16:501–514. doi: 10.1200/jco.1998.16.2.501 [PubMed: 9469334]
7. Panjari M, Bell RJ, Davis SR (2011) Sexual function after breast cancer. J Sex Med 8:294–302. doi: 10.1111/j.1743-6109.2010.02034.x [PubMed: 21199377]
8. Schover LR (2019) Sexual quality of life in men and women after cancer. Climacteric 22:553–557. doi: 10.1080/13697137.2018.1526893 [PubMed: 30380961]
9. Thors CL, Broeckel JA, Jacobsen PB (2001) Sexual functioning in breast cancer survivors. Cancer Control 8:442–448. doi: 10.1177/107327480100800508 [PubMed: 11579341]
10. Wiggins DL, Wood R, Granai CO, Dizon DS (2007) Sex, intimacy, and the gynecologic oncologists: survey results of the New England Association of Gynecologic Oncologists (NEAGO). J Psychosoc Oncol 25:61–70. doi: 10.1300/J077v25n04_04 [PubMed: 18032265]
11. Brédart A, Dolbeault S, Savignoni A, Besancenet C, This P, Giami A, Michaels S, Flahault C, Falcou MC, Asselain B, Copel L (2011) Prevalence and associated factors of sexual problems after early-stage breast cancer treatment: results of a French exploratory survey. Psychooncology 20:841–850. doi: 10.1002/pon.1789 [PubMed: 20568085]
12. Fouladi N, Feizi I, Nadermohammadi M, Mehrara E, Adldoosti R, Alimohammadi S (2021) The Predictors of Sexual Satisfaction among Iranian Women with Breast Cancer. Asian Pac J Cancer Prev 22:391–396. doi: 10.31557/apjcp.2021.22.2.391 [PubMed: 33639652]
13. Ooi PS, Draman N, Muhamad R, Yusoff SSM, Noor NM, Haron J, Hadi ISA (2021) Sexual Dysfunction Among Women With Breast Cancer in the Northeastern Part of West Malaysia. Sex Med 9:100351. doi: 10.1016/j.esxm.2021.100351 [PubMed: 34030061]
14. Basson R (2001) Female sexual response: the role of drugs in the management of sexual dysfunction. Obstet Gynecol 98:350–353. doi: 10.1016/s0029-7844(01)01452-1 [PubMed: 11506856]
15. Sand M, Fisher WA (2007) Women's endorsement of models of female sexual response: the nurses' sexuality study. J Sex Med 4:708–719. doi: 10.1111/j.1743-6109.2007.00496.x [PubMed: 17498106]
16. American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders American Psychiatric Press, Arlington, VA
17. Krychman M, Millheiser LS (2013) Sexual health issues in women with cancer. J Sex Med 10 Suppl 1:5–15. doi: 10.1111/jsm.12034 [PubMed: 23387907]
18. Sears CS, Robinson JW, Walker LM (2018) A comprehensive review of sexual health concerns after cancer treatment and the biopsychosocial treatment options available to female patients. Eur J Cancer Care (Engl) 27:e12738. doi: 10.1111/ecc.12738 [PubMed: 28795458]
19. Sekse RJ, Råheim M, Gjengedal E (2015) Shyness and openness--common ground for dialogue between health personnel and women about sexual and intimate issues after gynecological cancer. Health Care Women Int 36:1255–1269. doi: 10.1080/07399332.2014.989436 [PubMed: 25424412]
20. Dizon DS, Suzin D, McIlvenna S (2014) Sexual health as a survivorship issue for female cancer survivors. Oncologist 19:202–210. doi: 10.1634/theoncologist.2013-0302 [PubMed: 24396051]
21. Marwick C (1999) Survey says patients expect little physician help on sex. Jama 281:2173–2174. doi: 10.1001/jama.281.23.2173 [PubMed: 10376552]
22. Aerts L, Christiaens MR, Enzlin P, Neven P, Amant F (2014) Sexual functioning in women after mastectomy versus breast conserving therapy for early-stage breast cancer: a prospective controlled study. Breast 23:629–636. doi: 10.1016/j.breast.2014.06.012 [PubMed: 25082211]

23. Biglia N, Moggio G, Peano E, Sgandurra P, Ponzone R, Nappi RE, Sismondi P (2010) Effects of surgical and adjuvant therapies for breast cancer on sexuality, cognitive functions, and body weight. J Sex Med 7:1891–1900. doi: 10.1111/j.1743-6109.2010.01725.x [PubMed: 20233281]
24. Gandhi C, Butler E, Pesek S, Kwait R, Edmonson D, Raker C, Clark MA, Stuckey A, Gass J (2019) Sexual Dysfunction in Breast Cancer Survivors: Is it Surgical Modality or Adjuvant Therapy? Am J Clin Oncol 42:500–506. doi: 10.1097/coc.0000000000000552 [PubMed: 31094713]
25. Chang CP, Chen Y, Blackburn B, Abdelaziz S, Rowe K, Snyder J, Dodson M, Deshmukh V, Newman M, Stanford JB, Porucznik CA, Ose J, Fraser A, Smith K, Doherty J, Gaffney D, Hashibe M (2020) Genitourinary disease risks among ovarian cancer survivors in a population-based cohort study. Gynecol Oncol 157:529–535. doi: 10.1016/j.ygyno.2020.02.028 [PubMed: 32122688]
26. Hu Q, Chang CP, Rowe K, Snyder J, Deshmukh V, Newman M, Fraser A, Smith K, Gren LH, Porucznik C, Stanford JB, Gaffney D, Henry NL, Lopez I, Hashibe M (2021) Disparities in Cardiovascular Disease Risk Among Hispanic Breast Cancer Survivors in a Population-Based Cohort. JNCI Cancer Spectr 5. doi: 10.1093/jncics/pkab016
27. Isac C, Lee P, Arulappan J (2021) Older adults with chronic illness - Caregiver burden in the Asian context: A systematic review. Patient Educ Couns doi: 10.1016/j.pec.2021.04.021
28. Hernan MA, Hernandez-Diaz S, Werler MM, Mitchell AA (2002) Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. Am J Epidemiol 155:176–184. doi: 10.1093/aje/155.2.176 [PubMed: 11790682]
29. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383. [PubMed: 3558716]
30. Lambert PC, Royston P (2009) Further development of flexible parametric models for survival analysis. Stata J 9:265–290. doi: Doi 10.1177/1536867x0900900206
31. Orsini N (2013) Review of Flexible Parametric Survival Analysis Using Stata: Beyond the Cox Model by Patrick Royston and Paul C. Lambert. Stata J 13:212–216. doi: Doi 10.1177/1536867×1301300115
32. Gass JS, Onstad M, Pesek S, Rojas K, Fogarty S, Stuckey A, Raker C, Dizon DS (2017) Breast-Specific Sensuality and Sexual Function in Cancer Survivorship: Does Surgical Modality Matter? Ann Surg Oncol 24:3133–3140. doi: 10.1245/s10434-017-5905-4 [PubMed: 28608119]
33. Sbitti Y, Kadiri H, Essaidi I, Fadoukhair Z, Kharmoun S, Slimani K, Ismaili N, Ichou M, Errihani H (2011) Breast cancer treatment and sexual dysfunction: Moroccan women's perception. BMC Womens Health 11:29. doi: 10.1186/1472-6874-11-29 [PubMed: 21668971]
34. Baumgart J, Nilsson K, Evers AS, Kallak TK, Poromaa IS (2013) Sexual dysfunction in women on adjuvant endocrine therapy after breast cancer. Menopause 20:162–168. doi: 10.1097/gme.0b013e31826560da [PubMed: 22990756]
35. Albornoz CR, Matros E, McCarthy CM, Klassen A, Cano SJ, Alderman AK, VanLaeken N, Lennox P, Macadam SA, Disa JJ, Mehrara BJ, Cordeiro PG, Pusic AL (2014) Implant breast reconstruction and radiation: a multicenter analysis of long-term health-related quality of life and satisfaction. Ann Surg Oncol 21:2159–2164. doi: 10.1245/s10434-014-3483-2 [PubMed: 24740825]
36. Szegda KL, Whitcomb BW, Purdue-Smithe AC, Boutot ME, Manson JE, Hankinson SE, Rosner BA, Bertone-Johnson ER (2017) Adult adiposity and risk of early menopause. Hum Reprod 32:2522–2531. doi: 10.1093/humrep/dex304 [PubMed: 29087465]
37. Tao X, Jiang A, Yin L, Li Y, Tao F, Hu H (2015) Body mass index and age at natural menopause: a meta-analysis. Menopause 22:469–474. doi: 10.1097/gme.0000000000000324 [PubMed: 25203893]
38. Desmedt C, Fornili M, Clatot F, Demicheli R, De Bortoli D, Di Leo A, Viale G, de Azambuja E, Crown J, Francis PA, Sotiriou C, Piccart M, Biganzoli E (2020) Differential Benefit of Adjuvant Docetaxel-Based Chemotherapy in Patients With Early Breast Cancer According to Baseline Body Mass Index. J Clin Oncol 38:2883–2891. doi: 10.1200/jco.19.01771 [PubMed: 32614702]
39. Pajares B, Pollán M, Martín M, Mackey JR, Lluch A, Gavila J, Vogel C, Ruiz-Borrego M, Calvo L, Pienkowski T, Rodríguez-Lescure Á, Seguí MA, Tredan O, Antón A, Ramos M, Cámara Mdel

C, Rodríguez-Martín C, Carrasco E, Alba E (2013) Obesity and survival in operable breast cancer patients treated with adjuvant anthracyclines and taxanes according to pathological subtypes: a pooled analysis. Breast Cancer Res 15:R105. doi: 10.1186/bcr3572 [PubMed: 24192331]

40. Cornell LF, Mussallem DM, Gibson TC, Diehl NN, Bagaria SP, McLaughlin SA (2017) Trends in Sexual Function After Breast Cancer Surgery. Ann Surg Oncol 24:2526–2538. doi: 10.1245/s10434-017-5894-3 [PubMed: 28560595]
41. Carter J, Lacchetti C, Andersen BL, Barton DL, Bolte S, Damast S, Diefenbach MA, DuHamel K, Florendo J, Ganz PA, Goldfarb S, Hallmeyer S, Kushner DM, Rowland JH (2018) Interventions to Address Sexual Problems in People With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Adaptation of Cancer Care Ontario Guideline. J Clin Oncol 36:492–511. doi: 10.1200/jco.2017.75.8995 [PubMed: 29227723]
42. Halley MC, May SG, Rendle KA, Frosch DL, Kurian AW (2014) Beyond barriers: fundamental 'disconnects' underlying the treatment of breast cancer patients' sexual health. Cult Health Sex 16:1169–1180. doi: 10.1080/13691058.2014.939227 [PubMed: 25138386]
43. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, Ferguson D, D'Agostino R Jr. (2000) The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 26:191–208. doi: 10.1080/009262300278597 [PubMed: 10782451]
44. Taylor S, Harley C, Ziegler L, Brown J, Velikova G (2011) Interventions for sexual problems following treatment for breast cancer: a systematic review. Breast Cancer Res Treat 130:711–724. doi: 10.1007/s10549-011-1722-9 [PubMed: 21904884]
45. Steinauer J, LaRochelle F, Rowh M, Backus L, Sandahl Y, Foster A (2009) First impressions: what are preclinical medical students in the US and Canada learning about sexual and reproductive health? Contraception 80:74–80. doi: 10.1016/j.contraception.2008.12.015 [PubMed: 19501219]
46. Warner C, Carlson S, Crichlow R, Ross MW (2018) Sexual Health Knowledge of U.S. Medical Students: A National Survey. J Sex Med 15:1093–1102. doi: 10.1016/j.jsxm.2018.05.019 [PubMed: 30017717]
47. Rubin ES, Rullo J, Tsai P, Criniti S, Elders J, Thielen JM, Parish SJ (2018) Best Practices in North American Pre-Clinical Medical Education in Sexual History Taking: Consensus From the Summits in Medical Education in Sexual Health. J Sex Med 15:1414–1425. doi: 10.1016/j.jsxm.2018.08.008 [PubMed: 30297093]
48. Shindel AW, Parish SJ (2013) Sexuality education in North American medical schools: current status and future directions. J Sex Med 10:3–17; quiz 18. doi: 10.1111/j.1743-6109.2012.02987.x
49. Bober SL, Reese JB, Barbera L, Bradford A, Carpenter KM, Goldfarb S, Carter J (2016) How to ask and what to do: a guide for clinical inquiry and intervention regarding female sexual health after cancer. Curr Opin Support Palliat Care 10:44–54. doi: 10.1097/spc.0000000000000186 [PubMed: 26716390]
50. Flynn KE, Lindau ST, Lin L, Reese JB, Jeffery DD, Carter J, Baron SR, Abramsohn E, Weinfurt KP (2015) Development and Validation of a Single-Item Screener for Self-Reporting Sexual Problems in U.S. Adults. J Gen Intern Med 30:1468–1475. doi: 10.1007/s11606-015-3333-3 [PubMed: 25893421]
51. McGahuey CA, Gelenberg AJ, Laukes CA, Moreno FA, Delgado PL, McKnight KM, Manber R (2000) The Arizona Sexual Experience Scale (ASEX): reliability and validity. J Sex Marital Ther 26:25–40. doi: 10.1080/009262300278623 [PubMed: 10693114]

Table 1.

Characteristics of female breast cancer survivors and general population cohorts

	Breast cancer survivors (n=19,709)		General population (n=93,389)		P for chi-square
	n	%	n	%	
Race					<0.001
White	18,759	95.2	88,030	94.3	
Black or African American	57	0.3	257	0.3	
Asian	249	1.3	829	0.9	
Native Hawaiian and other Pacific Islanders	74	0.4	192	0.2	
Native American	~	~	502	0.5	
Multiple races	539	2.7	1,961	2.1	
Unknown	~	~	1,618	1.7	
Hispanic					<0.001
No	17,623	89.4	71,236	76.3	
Yes	1,980	10.0	7,407	7.9	
Unknown	106	0.5	14,746	15.8	
Age at cancer diagnosis or baseline					0.014
18 to 45	2,820	14.3	13,656	14.6	
45 to 54	4,475	22.7	21,652	23.2	
55 to 64	4,957	25.2	23,717	25.4	
65 to 74	4,221	21.4	19,911	21.3	
75 to 101	3,236	16.4	14,453	15.5	
Education					<0.001
Some high school or less	1,953	9.9	10,190	10.9	
High school degree	4,549	23.1	24,715	26.5	
Some college	4,239	21.5	22,992	24.6	
College degree or higher	3,347	17.0	16,495	17.7	
Unknown	5,621	28.5	18,997	20.3	
Baseline BMI [a]					<0.001
<18.5 kg/m^2	367	1.9	2,020	2.2	
18.5 to 24.9 kg/m^2	8,811	44.7	42,607	45.6	
25 to 29.9 kg/m^2	6,245	31.7	28,105	30.1	
30+ kg/m^2	4,286	21.7	20,657	22.1	
Baseline Charlson Comorbidity Index					0.085
0	11,963	60.7	57,422	61.5	
1	4,179	21.2	19,224	20.6	
2+	3,567	18.1	16,743	17.9	
First degree family history of breast cancer					<0.001
No	16,786	85.2	83,753	89.7	
Yes	2,923	14.8	9,636	10.3	

Abbreviation: BMI, body mass index

[a] Imputed BMI

[~] Counts and percentage are suppressed if fewer than 11

Table 2.

Clinical characteristics of female breast cancer survivors, diagnosed from 1997 to 2017 (n=19,709)

Clinical characteristics	N	%
Year of cancer diagnosis		
1997–2001	3,929	19.9
2002–2006	4,100	20.8
2007–2011	4,846	24.6
2012–2017	6,834	34.7
Cancer Stage		
Localized	12,133	61.6
Regional	6,867	34.8
Distant	709	3.6
Residence [a]		
Urban	17,345	88.0
Rural	2,356	12.0
ER status		
ER+	15,492	78.6
ER−	3,402	17.3
Unknown	815	4.1
PR status		
PR+	13,493	68.5
PR−	5,230	26.5
Unknown	986	5.0
HER2 [b]		
Positive	1,374	15.5
Negative	7,104	80.0
Unknown	397	4.5
Histology		
Ductal carcinoma	14,459	73.4
Lobular carcinoma	3,674	18.6
Mucinous carcinoma	456	2.3
Medullary carcinoma	104	0.5
Other type or unknown	1,016	5.2
Received surgery	19,021	96.5
Received radiotherapy	11,074	56.2
Received chemotherapy	8,391	42.6
Received immunotherapy	781	4.0
Received hormone therapy	8,327	42.2

Abbreviation: ER, estrogen receptors; PR, progesterone receptors; HR, hormone receptor; HER2, human epidermal growth factor receptor 2

[a] Eight breast cancer patients had missing residence information

[b] Available for the breast cancer patients diagnosed from 2010 to 2017

Table 3.

The risk of sexual dysfunction among breast cancer survivors compared to women from the general population

	All time periods (>1 year after cancer diagnosis or baseline)					>1 to 5 years after cancer diagnosis or baseline					>5 years after cancer diagnosis or baseline				
	Breast cancer survivors		General population		Hazard Ratio (95% CI)[a]	Breast cancer survivors		General population		Hazard Ratio (95% CI)[a]	Breast cancer survivors		General population		Hazard Ratio (95% CI)[a]
	N	%	N	%		N	%	N	%		N	%	N	%	
Sexual function symptoms [b]															
No	15,956	90.9	70,369	93.1	Reference	16,652	94.9	73,497	97.3	Reference	10,262	93.7	40,917	94.2	Reference
Yes	1,600	9.1	5,180	6.9	**1.60 (1.51, 1.70)**	904	5.1	2,052	2.7	**2.05 (1.89, 2.22)**	693	6.3	2,526	5.8	**1.24 (1.13, 1.35)**
Dyspareunia															
No	19,275	99.2	90,427	99.4	Reference	19,336	99.5	90,717	99.8	Reference	12,628	99.5	55,263	99.6	Reference
Yes	165	0.8	510	0.6	**1.79 (1.49, 2.15)**	104	0.5	220	0.2	**2.37 (1.87, 3.01)**	61	0.5	243	0.4	1.25 (0.94, 1.67)
Vaginal Dryness/Atrophic Vaginitis															
No	16,868	93.0	75,538	94.6	Reference	17,448	96.2	78,173	97.9	Reference	10,872	95.0	44,522	95.3	Reference
Yes	1,261	7.0	4,334	5.4	**1.51 (1.41, 1.61)**	681	3.8	1,699	2.1	**1.87 (1.71, 2.05)**	577	5.0	2,173	4.7	**1.22 (1.10, 1.34)**
Vaginal Complication															
No	18,654	97.0	87,918	98.2	Reference	18,892	98.3	88,871	99.3	Reference	12,235	98.1	53,385	98.5	Reference
Yes	571	3.0	1,566	1.8	**2.04 (1.84, 2.26)**	333	1.7	613	0.7	**2.76 (2.40, 3.17)**	238	1.9	799	1.5	**1.47 (1.26, 1.72)**
Decreased libido															
No	19,583	99.6	92,595	99.7	Reference	19,604	99.7	92,754	99.9	Reference	12,854	99.8	56,739	99.8	Reference
Yes	80	0.4	276	0.3	**1.48 (1.14, 1.92)**	59	0.3	117	0.1	**2.49 (1.79, 3.47)**	21	0.2	142	0.2	0.67 (0.42, 1.09)

Abbreviation: CI, confidence interval

[a] Models adjusted for matching factors (birth year and birth state), race/ethnicity, baseline body mass index, baseline Charlson Comorbidity Index

[b] Included dyspareunia, vaginal dryness and complication, decreased libido, lack of arousal, lack of orgasm, other sexual dysfunction

Table 4.

The risk of sexual dysfunction among breast cancer survivors compared to women from the general population stratified by age at cancer diagnosis, >1 to 5 years after cancer diagnosis

	<50 years old at cancer diagnosis					50− <65 years old at cancer diagnosis					65+ years old at cancer diagnosis				
	Breast cancer survivors		General population		Hazard Ratio (95% CI)[a]	Breast cancer survivors		General population		Hazard Ratio (95% CI)[a]	Breast cancer survivors		General population		Hazard Ratio (95% CI)[a]
	N	%	N	%		N	%	N	%		N	%	N	%	
Sexual function symptoms															
No	3,933	91.8	17,841	97.0	Reference	6,184	94.7	27,814	97.1	Reference	6,535	96.9	27,842	97.6	Reference
Yes	351	8.2	555	3.0	**3.05 (2.65, 3.51)**	347	5.3	821	2.9	**1.98 (1.74, 2.26)**	206	3.1	676	2.4	**1.36 (1.16, 1.60)**
Dyspareunia															
No	4,765	98.8	22,714	99.5	Reference	7,156	99.5	33,981	99.7	Reference	7,415	99.9	34,022	99.9	Reference
Yes	60	1.2	104	0.5	**2.89 (2.08, 4.03)**	35	0.5	92	0.3	**1.95 (1.31, 2.91)**	~	~	24	0.1	2.35 (0.96, 5.72)
Vaginal Dryness/Atrophic Vaginitis															
No	4,285	95.1	19,715	98.1	Reference	6,476	95.9	29,637	97.7	Reference	6,687	97.3	28,821	97.9	Reference
Yes	221	4.9	392	1.9	**2.81 (2.37, 3.33)**	276	4.1	693	2.3	**1.85 (1.60, 2.14)**	184	2.7	614	2.1	**1.34 (1.13, 1.59)**
Vaginal Complication															
No	4,619	96.8	22,288	99.0	Reference	7,014	98.3	33,485	99.4	Reference	7,259	99.2	33,098	99.5	Reference
Yes	153	3.2	219	1.0	**3.67 (2.95, 4.56)**	124	1.7	211	0.6	**2.89 (2.30, 3.64)**	56	0.8	183	0.5	**1.52 (1.11, 2.08)**
Decreased libido															
No	4,889	99.2	23,711	99.8	Reference	7,272	99.8	34,786	99.9	Reference	7,443	99.9	34,257	100.0	Reference
Yes	37	0.8	59	0.2	**3.09 (2.00, 4.77)**	17	0.2	46	0.1	**1.96 (1.09, 3.53)**	~	~	12	0.0	1.66 (0.48, 5.70)

Abbreviation: CI, confidence interval

[a] Models adjusted for matching factors (birth year and birth state), race/ethnicity, baseline body mass index, baseline Charlson Comorbidity Index

[b] Included dyspareunia, vaginal dryness and complication, decreased libido, lack of arousal, lack of orgasm, other sexual dysfunction

~ Counts and percentage are suppressed if fewer than 11

Table 5.

Risk factors for sexual function symptoms among breast cancer survivors >1 year after cancer diagnosis

	HR (95% CI)
ER status [a]	
Negative	Reference
Positive	**1.29 (1.12, 1.48)**
Radiotherapy [a]	
No	Reference
Yes	**1.17 (1.06, 1.30)**
Chemotherapy [a]	
No	Reference
Yes	**1.16 (1.03, 1.30)**
Endocrine therapy [a]	
No	Reference
Yes	**1.46 (1.32, 1.62)**
Cancer Stage [b]	
Localized	Reference
Regional	1.11 (1.00, 1.23)
Distant	0.70 (0.46, 1.07)
Baseline Charlson Comorbidity Index [c]	
0	Reference
1	**1.42 (1.25, 1.60)**
2+	**1.53 (1.30, 1.80)**
Baseline body mass index (BMI) [d]	
<18.5 kg/m^2	1.12 (0.82, 1.54)
18.5 to 24.9 kg/m^2	Reference
25 to 29.9 kg/m^2	**0.85 (0.75, 0.95)**
30+ kg/m^2	**0.77 (0.67, 0.89)**
Ethnicity [e]	
Non-Hispanic	Reference
Hispanic	0.97 (0.82, 1.14)
Age [f]	
<50	Reference
>=50	**1.69 (1.52, 1.88)**
Residence [a]	
Urban	Reference
Rural	1.02 (0.88, 1.19)

Abbreviation: HR, hazard ratio; CI, confidence interval

[a.] Models adjusted for age at cancer diagnosis, year of cancer diagnosis, race/ethnicity, baseline BMI, baseline Charlson Comorbidity Index, cancer stage;

[b] Models adjusted for age at cancer diagnosis, year of cancer diagnosis, race/ethnicity, baseline BMI, baseline Charlson Comorbidity Index;

[c] Models adjusted for age at cancer diagnosis, race/ethnicity, baseline BMI

[d] Models adjusted for age at cancer diagnosis, race/ethnicity, baseline Charlson Comorbidity Index;

[e] Models adjusted for age at cancer diagnosis, year of cancer diagnosis, race, baseline BMI, baseline Charlson Comorbidity Index; f. Models adjusted for year of cancer diagnosis, race, baseline BMI, baseline Charlson Comorbidity Index