Clinical Trial Note

Impact of modifiable lifestyle factors on outcomes after breast cancer diagnosis: the Setouchi Breast Cancer Cohort Study

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Abstract

The primary purpose of this large cohort study is to investigate the effects on breast cancer outcomes of modifiable lifestyle factors after breast cancer diagnosis. These factors include physical activity, smoking, alcohol consumption, obesity and weight gain after diagnosis, alternative medicine and dietary factors. Women diagnosed with Stage 0 to III breast cancer are eligible for participation to this study. Lifestyle, use of alternative medicine, psychosocial factors, reproductive factors and health-related quality of life will be assessed using a questionnaire at the time of breast cancer diagnosis (baseline), and 1, 2, 3 and 5 years after diagnosis. Clinical information and breast cancer outcomes will be obtained from a breast cancer database. The primary endpoint will be disease-free survival. Secondary endpoints are overall survival, health-related quality of life, breast cancer-related symptoms and adverse events. Patient recruitment commenced in February 2013. Enrollment of 2000 breast cancer patients is planned during the 5-year recruitment period. The concept of the study is described in this article.

Key words: breast cancer, cohort study, lifestyle, alternative medicine, prognosis, quality of life

Introduction

The incidence of breast cancer in women has tended to increase since 1975 in Japan, and the number of newly diagnosed cases of breast cancer, including carcinoma in situ, was 76,041 in 2010 (1). The crude and age-adjusted incidence of breast cancer, including carcinoma in situ, in 2010 was 115.7 and 88.7 per 0.1 million population, which was the highest among all cancers. Japanese vital statistics (Ministry of Health, Labour and Welfare) show that mortality from breast cancer has also increased consistently since the 1960s. The number of deaths due to breast cancer in women was 13,148 in 2013. The crude and
Summary of the study protocol

Purpose
The primary purpose of this study is to investigate the effects on breast cancer outcomes of modifiable lifestyle factors after breast cancer diagnosis. These factors include physical activity, smoking, alcohol consumption, obesity and weight gain after diagnosis and dietary factors. The secondary purpose is to evaluate the status of breast cancer survivors, including physical, functional, social and psychological well-being, and the needs of survivors after diagnosis.

Study setting
The Setouchi Breast Cancer Cohort Study (SBCCS) is a multi-institutional prospective cohort study with 15 participating centers, as of 7 April 2014.

Study support
This study is supported by the Non-Profit Organization Setouchi Breast Project Comprehensive Support (SBP-CS). Data management is supported by the Non-Profit Organization Japan Clinical Research Support Unit (J-CRSU).

Endpoints
The primary endpoint of the SBCCS is disease-free survival (DFS), defined as the time from enrollment to the earliest documentation of disease relapse, asynchronous breast cancer, any secondary cancer or death due to any cause. Secondary endpoints include overall survival (OS), health-related quality of life (HRQoL), breast cancer-related symptoms and adverse events.

Eligibility criteria
Inclusion criteria
(i) Histological or cytological diagnosis of breast cancer and planned radical treatment for the disease at a participating institution.

(ii) Women aged ≥ 20 years old.

(iii) Signed written informed consent.

Exclusion criteria
(i) Breast cancer with distant metastasis (Stage IV).

(ii) Ineligibility for the study based on the decision of an investigator.

Registration and treatment
The SBP-CS office will confirm patient eligibility and assign an anonymous number to each patient. Breast cancer treatment is not prescribed in the SBCCS and depends on the choice of each patient and physician.

Assessments
Lifestyle
Lifestyle at the time of and after breast cancer diagnosis will be assessed using a self-reported questionnaire developed in the Japan Public Health Center-based Prospective Study (JPHC study). This questionnaire was validated in healthy adults and has been proven to be useful for assessment of physical activity, smoking, alcohol consumption and dietary factors. Other lifestyle factors, such as bathing, sleeping habit, bowel movements, internet use and social activity, will be assessed using original questionnaire items.

Psychosocial factors
Psychosocial factors will be assessed using the Public Health Research Foundation—Stress Check List (PHRF-SCL), Stress-Coping Assessment Questionnaire, Health Hope Index, Perceived Positive Change and Hospital Anxiety and Depression Scale.

Social background and reproductive factors
Marital status, children, presence of partner, household income, educational background and work status will be assessed using original items. Menstrual status at the time of and after breast cancer diagnosis, and reproductive and breastfeeding history will also be assessed using original items.

HRQoL and patient-reported symptoms
HRQoL will be assessed using established questionnaires: the Functional Assessment of Cancer Therapy (FACT)-Endocrine Symptoms (ES), -Breast (B) and -Taxane; and the MOS 36-Item Short-Form Health Survey (SF36®). Cancer-related fatigue will be assessed using the Cancer Fatigue Scale. Chemotherapy-induced peripheral neurotoxicity will be assessed using the Patient Neurotoxicity Questionnaire (PNO). Breast cancer-related symptoms will be assessed using 25 items on an original self-reported symptoms checklist developed for this study.

Other factors
The status of use of alternative medicine after breast cancer diagnosis and the informational and supportive needs of patients at each time point will be assessed using original items.

Evaluation points
The evaluation time points for each questionnaire are at registration (baseline) and at 1, 2, 3 and 5 years after registration.
Clinical factors
Clinical information including clinical and pathological stage, tumor subtype, treatment factors and breast cancer outcomes (events related to DFS and OS) will be obtained from a database, which is referred to as the Setouchi Breast Cancer Registry (SBCR). The SBCR will be administered by the breast cancer registration committee of the SBP-CS. Use of SBCR data for research has been approved by the institutional ethics committee on human research at Okayama University.

Statistical analysis
Main analysis
The primary purpose of this study is to investigate the effect of modifiable lifestyle factors, alternative medicine and dietary factors after breast cancer diagnosis on breast cancer outcomes (DFS, OS and HRQoL). Thus, the main analysis will focus on the relationship between each factor and breast cancer outcomes. For breast cancer outcomes that are time-to-event based, such as DFS and OS, survival of groups classified by data for potential factors will be estimated using the Kaplan–Meier method and compared by the log-rank test. A Cox proportional hazard regression model will be used for multivariate analysis. Breast cancer outcomes that involve binary data, such as the rate of adverse events in each group, will be compared by $\chi^2$-test. Breast cancer outcomes based on quantitative data, such as the HRQoL score in each group, will be compared by $t$-test or analysis of variance. In multivariate analysis, a generalized estimating equation will be used.

Sample size and follow-up period
The target sample size of this study is 2000, the registration period is 5 years and the follow-up period is 5 years after the last patient registration. With this sample size and study duration, and with the assumption that the rate of each factor is 50% over all subjects, an assumed 10-year DFS of 80% in the group that is negative for a particular factor and a significance level of 5% gives detection powers of 89% for a hazard ratio (HR) of 1.5, 77% for a HR of 1.4 and 58% for a HR of 1.3. Similarly, an assumed 10-year DFS of 70% in the same group results in detection powers of 98, 92 and 76% for HRs of 1.5, 1.4 and 1.3, respectively. Thus, this sample size and follow-up period are sufficient to detect factors with a HR $\geq$1.3. The study cannot detect factors with HR $\leq$1.2 and a further study or combined analysis with another study will be needed for these factors.

This study was approved by the institutional ethics committee on human research at Okayama University on September 2012. The study was started in February 2013 and completion is scheduled for February 2023.

Registration of the protocol
The protocol of SBCCS was registered at the website of the University Hospital Medical Information Network (UMIN), Japan (protocol ID UMIN000013647), on 7 April 2014. Details are available at https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=browse&action=browse&type=summary&recptno=R000015929&language=J.

Discussion
The Evidence-based Breast Cancer Clinical Guidelines for Epidemiology and Prevention of the Japanese Breast Cancer Society reviewed reports on the association of prognosis with obesity, intake of fat, alcohol, isoflavones and dairy products; physical activity and smoking after diagnosis of breast cancer (4). These guidelines concluded that obesity at diagnosis was a ‘convincing’ factor that worsens breast cancer prognosis, obesity after diagnosis was a ‘probable’ factor for a worsened prognosis and physical activity after diagnosis was a ‘probable’ factor for an improved prognosis. However, other lifestyle factors were judged to be ‘limited-suggestive’ or ‘limited-no conclusion’ based on the lack of an established association between prognosis and these factors after diagnosis of breast cancer, and the absence of high-quality studies. Thus, this study will provide informative evidence for breast cancer survivors or caregivers regarding optimal lifestyle after breast cancer diagnosis.

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Conflict of interest statement
None declared.

References