Adverse Health-Related Outcomes of Treatment in an Israeli Cohort of Breast Cancer Survivors

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ABSTRACT

Background: Recent improvements in cancer survival are largely due to earlier diagnosis and advancements in treatment. However, many survive only to be faced with another debilitating illness that is absent or subclinical at the end of therapy. Long-term breast cancer survivors might be at increased risk of cardiovascular disease, second malignancy, osteoporosis and fractures, diabetes and other gruelling disabilities. At best, about half of these patients are likely to suffer unendurable long-lasting pain that can have a profound negative impact on their physical and psychosocial lives. Despite the massive reporting on adverse health-related outcomes in the last two decades, the association with breast cancer treatment regimens is still limited.

Aim: The study aims to investigate the relationship between breast cancer treatment regimens and incidence of health-related adverse outcomes, in order to identify at-risk group of patients that require aggressive monitoring, follow-up and support to optimize survival and minimize the potential for increased treatment-related morbidity.

Methods: Patient-based case-cohort study of 1-year female survivors of invasive breast cancer, members of Leumit Health Services (LHS), a health maintenance organization in Israel, between 2003 and 2010. LHS databases include approximately 4,200 patients diagnosed with malignant neoplasm of female breast during this period, with mean age of 60±13 years at time of diagnosis. A random sample of the study population at a sampling fraction of 10% will be selected at the outset of the study. This subcohort will constitute the control group for the cardiovascular disease, second malignant neoplasm, osteoporosis and bone fractures, and diabetes outcome studies. In the next step, we will identify all outcome cases (nonsubcohort and subcohort) and compare treatments received with the subcohort. Follow-up will start from time of breast cancer diagnosis until the date of outcome diagnosis, and will be censored at time of death, LHS disenrollment, or the predetermined censoring date set to December 31, 2014, whichever occurs earlier. In addition, a cross-sectional retrospective study will be performed to assess treatment effect on the quality of

life and the development of chronic pain and related sequelae among breast cancer survivors.
The computerized database of LHS and linkage of the total cohort with additional national databases, such as the National Mortality database and that of the Israel National Cancer Registry (INCR), will provide information on exposures, outcomes, and potential confounders. Breast cancer survivors will be interviewed by telephone or sent self-administered questionnaires on pain, lifestyle and work behaviors as well.
In order to determine the independent impact of treatment regimens on risk of adverse health-related outcomes, multiple regression models will be constructed, adjusting for patient sociodemographic, clinical, and behavioral characteristics. Multiple sensitivity analyses will be performed to substantiate the robustness of results, including a propensity analysis for addressing the issue of nonrandom allocation to treatment, or reassessment of treatment effects among all survivors to ensure not introducing survival bias.
Informed consent forms signed by patients and ethics approval from the institutional review boards of LHS and Haifa University will be obtained.
Expected results: Radiotherapy will be the major treatment regimen responsible for inducing chronic pain and second primary cancers, especially in those anatomical locations at the vicinity of the irradiation field. Chemotherapy will play the principal role in cardiotoxicity development, secondary leukemias and bone turnover, whereas hormone therapy will exacerbate risk of diabetes.
Significance: Information currently available on breast cancer treatment late effects, diabetes in particular, is limited, inconsistent, and inconclusive. To fill this gap of knowledge and substantiate evidence needed for planning and implementing cost-effective follow-up plans in routine clinical practice, the proposed study is intended to follow on a cohort of breast cancer survivors long enough to fully capture the detrimental impact of cancer treatment.