



Detection of a negative correlation between prescription of Chinese herbal products containing coumestrol, genistein or daidzein and risk of subsequent endometrial cancer among tamoxifen-treated female breast cancer survivors in Taiwan between 1998 and 2008: A population-based study

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ABSTRACT

Ethnopharmacological relevance: Tamoxifen users sometimes seek complementary and alternative medicine advice for treatment of a variety of illness and co-administer with *phytoestrogen*-containing herbs, resulting in an increasing concern of its influence in subsequent endometrial cancer risk. Our study aims to determine the prevalence of Chinese herbal products containing coumestrol, genistein, or daidzein and their association with subsequent endometrial cancer risk among tamoxifen-treated breast cancer survivors in Taiwan.

Methods: We selected all patients who were newly diagnosed with invasive breast cancer and received tamoxifen treatment between January 1, 1998, and December 31, 2008, from the National Health Insurance Research Database. Among the 26,656 tamoxifen-treated breast cancer survivors, we evaluated the usage, frequency of service, and prescription of Chinese herbal products containing coumestrol, genistein, or daidzein. The logistic regression method was employed to calculate the odds ratios for utilization of those herbal products. Cox proportional hazard regression was set to calculate the hazard ratios of endometrial cancer associated with such usage.

Results: Of the patients surveyed, 36.2% ($n=9652$) of the tamoxifen-treated breast cancer survivors examined in the study had consumed Chinese herbal products containing coumestrol, genistein, or daidzein during the study period. Exposure to *Ge Gen* (*Puerariae Radix*) specifically was the most extensive. For it, the population consumed an average cumulative dose of above 180 g. Compared to those who had never used Chinese herbal products, breast cancer survivors who had taken Chinese herbal products containing coumestrol, genistein, or daidzein concurrently with tamoxifen treatment did not have a higher hazard ratio for subsequent development of endometrial cancer.

Conclusion: Among those tamoxifen-treated female breast cancer survivors in Taiwan, consumption of Chinese herbal products containing coumestrol, genistein, or daidzein is negatively correlated with subsequent endometrial cancer risk.

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Abbreviations: TMX, tamoxifen; BC, breast cancer; CHP, Chinese herbal products; CGD-CHPs, Chinese herbal products containing coumestrol, genistein and/or daidzein; WM, western medicine; TCM, Traditional Chinese medicine; NHI, National Health Insurance; NHIRD, National Health Insurance research database; DCMP, Department of Chinese Medicine and Pharmacy; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; DDD, defined daily dose; ORs, odd ratios; CI, confidence interval; aHR, adjusted hazard ratio

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1. Introduction

Tamoxifen (TMX) has been found to reduce the recurrence of contralateral breast tumors, which has led to its administration to patients of estrogen receptor positive (ER+) breast cancer (Bernstein et al., 1999; Van Leeuwen et al., 1994; Gelmon, 2000). It has recently been suggested that TMX treatment may increase the risk of endometrial carcinoma, most notably in breast cancer survivors (BC survivors) who are postmenopausal (Swerdlow et al., 2005; Cuzick et al., 2003; Hardell, 1988; Fornander et al., 1989;

Andersson et al., 1991; Fisher et al., 1994; Sasco, 1996; Mignotte et al., 1998; Early Breast Cancer Trialists' Collaborative Group, 1998; Bergman et al., 2000). We have reported previously that use of Chinese herbal products (CHPs) which may contain strong phytoestrogens such as coumestrol, genistein, and daidzein are widespread among Taiwanese female patients with the intention to treat diseases of the respiratory system, diseases of the musculoskeletal system and connective tissue or of the digestive system and so on (Wu et al., 2012).

Furthermore, recent studies have found that daidzein, one of the active components of phytoestrogens, exhibits estrogen-induced cell proliferation in the rat uterus and enhances proliferation of breast cancer cells (Leonardo et al., 2012; Unfer et al., 2004). However, it remains unclear whether these observations translate to an increased risk of endometrial cancer in human patients. As findings on this matter presents potentially significant implications for breast cancer survivors who are taking TMX and are pursuing CHPs, it is desirable to resolve the question of whether interaction between CHPs containing coumestrol, genistein, and/or daidzein (CGD-CHPs) and TMX might result in endometrial carcinogenicity.

Individuals in Taiwan are free to visit western medicine (WM) clinics or traditional Chinese medicine (TCM) clinics for health care. As the insurance coverage rate is up to 99%, the random sample that comprises the National Health Research Institute (NHI) research database can be considered representative of the general population of Taiwan. The assessment of the co-utilization of CGD-CHPs and WM resources in Taiwan can be comprehensive. Therefore, pharmaco-epidemiological research could be performed with National Health Research Institute, Longitudinal Health Insurance Database (NHIRD) (Lai et al., 2013; Lee et al., 2013; Chen et al., 2013). Our study's aims are to investigate the demographics and patterns of CGD-CHPs usage among TMX-treated BC survivors from a Taiwanese nationwide cohort and to explore the association between such use and subsequent endometrial cancer risk among these individuals. Our findings could elucidate the potential risk of endometrial cancer under the combined use of CGD-CHPs and TMX and thus be a guideline of the appropriate consumption of phytoestrogen-rich CHP.

2. Materials and methods

2.1. Data resources and study sample

Our study protocols were approved by the Institutional Review Board of the Taipei City Hospital. This population-based study was designed to determine the prevalence of CGD-CHPs among TMX-treated BC survivors. We also sought to explore the associations between BC survivors who had been prescribed CGD-CHPs and the occurrence of subsequent endometrial cancer in Taiwan between January 1, 1998, and December 31, 2008. NHIRD provided all these data. The NHIRD records contained demographic information for each gender or age. Information concerning the prescribed drugs and their dosages, including CHPs, was estimated. The diagnoses used in the NHIRD are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (Centers for Disease Control and Prevention, 2014).

The selection of study subjects was performed as follows (Fig. 1). All the data of these 1,000,000 individuals were randomly selected by the National Health Research Institute. Our study includes all patients who were newly diagnosed with invasive breast cancer. Invasive breast cancer had to have been proven by tissue pathology to qualify for the registry, so that the data are very reliable. The process of patient selection was performed in accordance with the flow chart shown in Fig. 1. Male subjects and

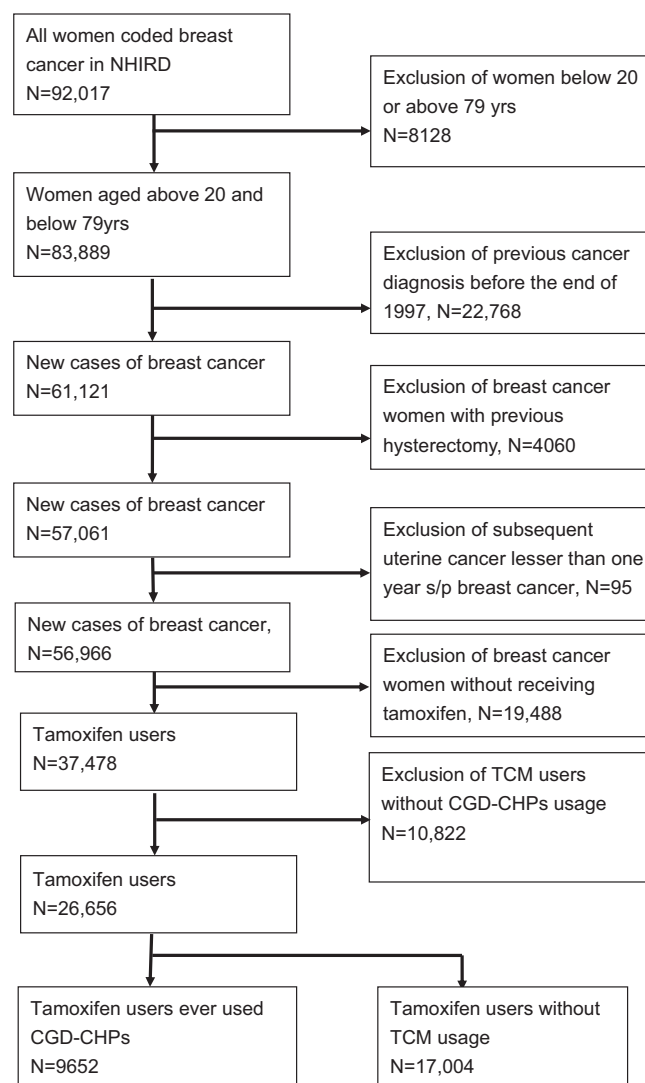


Fig. 1. Algorithm of recruitment of subjects from the National Health Insurance catastrophic illnesses registry of Taiwan and followed from 1998 to 2008.

patients who had never been diagnosed with breast cancer were ruled out ($n=907,983$). Second, cases who were under 20 or over 79 years of age ($n=8128$) were excluded. Next, we excluded the prevalent cases of any previous cancer diagnosis before 1997 ($n=22,768$). Then, we excluded those with previous hysterectomy ($n=4060$), subsequent uterine cancer less than one year *s/p* breast cancer ($n=95$), and those who had never received TMX ($n=19,488$). Subjects who had never consumed CGD-CHPs were also excluded ($n=10,822$). Here, we recruited all patients that had consumed CGD-CHPs that contained any of the following plant species, in accordance with our previous study: *Ge Gen* (Puerariae Radix), *Bu Gu Zhi* (Psoraleae Fructus), *Huai Hua* (Sophorae Flos), *Ku Shen Gen* (Sophorae Flavescentis Radix), *Dan Dou Chi* (Sojae Semen Praeparatum) (Wu et al., 2012). Finally, 26,656 TMX-treated BC survivors (non-TCM users, $n=17,004$; CGD-CHPs consumers, $n=9652$) were included in the study cohort.

2.2. Traditional Chinese medicine

The NHI of Taiwan reimburses a wide range of TCM treatments, including CHP, acupuncture, and manipulative therapies for trauma. CHPs form the most widely adopted TCM treatment used by patients in Taiwan (Hsieh et al., 2008). In order to study the utilization of prescribed CGD-CHPs, all the detailed herbal

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