European Journal of Oncology Nursing 19 (2015) 473–478

Contents lists available at ScienceDirect

European Journal of Oncology Nursing

journal homepage: www.elsevier.com/locate/ejon

Gynecological malignancy risk in colorectal cancer survivors: A population-based cohort study

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Keywords:
Colorectal cancer
Retrospective cohort study
Insurance data
Breast cancer
Endometrial cancer
Ovarian cancer

A B S T R A C T

Purpose: This study was carried out to assess the risk of gynecological malignancy in colorectal cancer survivors using a population-based retrospective cohort study.
Method: Using the National Health Insurance Research Database (NHIRD) of Taiwan, we identified 37,176 patients with colorectal cancer diagnosed in 1998–2009, aged 20 years and above, without other cancer history. We also randomly selected 148,700 women without any cancer in the comparison cohort, frequency matched by age and diagnosis date. Incidences and hazards of breast, cervix, endometrial and ovarian cancers were evaluated by 2011.
Results: The overall incidence of the 4 types of gynecological cancer was 39.0% higher in colorectal cancer patients than in comparisons (2.99 vs. 2.14 per 1000 person-years) with an adjusted hazard ratio (HR) of 1.46 (95% confidence interval (CI) = 1.31–1.62). Breast cancer accounted for most subsequent cancer. The multivariable Cox method measured HR was the highest for endometrial cancer (3.40, 95% CI = 2.59–4.47) for the colorectal cohort relative to comparisons, followed by ovarian cancer and breast cancer, except cervix cancer. The risk of gynecological malignancies was apparently elevated for colorectal cancer survivors <50 years of age.
Conclusions: Follow-up measures are suggested for women with colorectal cancer for early detection and prevention of the subsequent gynecological malignancy.

Introduction

Colorectal cancer is one of most common cancers in Taiwan, with a total of 14,040 new cases being reported in 2010. (http://www.bhp.doh.gov.tw) The risk of gynecological malignancy (ovarian, endometrial, and breast cancers) could be higher in women diagnosed previously with colorectal cancer because of diverse reasons including shared etiological factors, hereditary and environmental influences, and potential carcinogenic effects of prior treatments with chemotherapy or radiotherapy (Ng and Travis, 2008). With survival rates after diagnosis of numerous cancers continuing to improve, follow-up examinations of cancer survivors should not only consist of monitoring for local-regional and distant cancer recurrence, but should also include evaluations of health maintenance, life quality, and adverse effects of treatments, and surveillance for subsequent primary malignancy. Fortunately, for gynecological cancers, several identified etiological factors are amenable to preventive approaches.

To date, no studies have evaluated the risk of gynecological malignancy after colorectal cancer diagnosis. We aimed to assess whether women with prior colorectal cancer had an increased risk of developing gynecological malignancy, because if the risk of gynecological malignancy is higher in colorectal cancer survivors, early cancer detection and prevention measures should be advocated strongly.

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http://dx.doi.org/10.1016/j.ejon.2015.02.006
1462-3889/

Materials and methods

Data sources

This retrospective cohort study used the inpatient database and the registry for catastrophic illness database (RCID), a part of the National Health Insurance Research Database (NHIRD), established by the Bureau of National Health Insurance (NHI) on March 1, 1995. NHI program has a coverage rate over 99% for 23 million people in Taiwan and feature contracts with 90% of all health care facilities science 1996 (Lu et al., 2003 May–Jun). These databases included medical claims from 1996 to 2010 and information on beneficiaries. Diseases were defined based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). All insurance claims should be scrutinized by medical reimbursement specialists and peer review. The cancer diagnoses were based on the ICD-9 code determined by pathologic findings, therefore the cancer diagnoses in this study should be accurate and reliable. We confirm that all data were de-identified and analyzed anonymously. In addition, this study was also approved by the Ethics Review Committee at China Medical University (CMU-REC-101-012).

Study subjects

Fig. 1 shows the flow chart of selecting study cohorts. We selected 44,397 women with colorectal cancer (ICD-9-CM 153 and 154) from 1998 to 2009 from RCID. Exclusions were 1940 patients with a history of cancer (ICD-9-CM 140–152 and 155–208), 34 patients aged less than 20 years, and 5247 patients with a follow-up duration of <0.5 years. The remaining 37176 patients were included in the colorectal cancer group. The date with colorectal cancer diagnosed was used as entry date for estimating the follow-up time. Comparisons were selected from women without cancer history, including metastases (ICD-9-CM 196–199), solid cancer (ICD-9-CM 140–195) and hematopoietic cancer (ICD-9-CM 200–208) at the baseline. In order to increase the statistical power, 4-fold of controls were randomly selected, frequency-matched by age (stratified in 5-year durations) and entry date of the colorectal cancer case. To exclude certain control group members, we used the same criteria as those used for the colorectal cancer group.

Variables of interest

Study subjects were evaluated, from the entry date until the gynecologic cancers occurred, end of 2010, withdrew from the insurance or death. The female-specific cancers including breast (ICD-9-CM 174), cervical (ICD-9-CM 179), endometrial (ICD-9-CM 182), and ovarian (ICD-9-CM 183) cancers were evaluated. Comorbidity evaluation included diabetes (ICD-9-CM 250), hypertension (ICD-9-CM 401–405), dyslipidemia (ICD-9-CM 272) and hereditary colorectal polyposis (IC-9-CM 211.3), which were defined before the entry date.

Statistical analysis

All analyses were performed using SAS statistical software version 9.2 for Windows (SAS Institute Inc., Cary, NC, USA) and 2-sided $P < 0.05$ was considered significant. Demographic differences between the 2 cohorts were compared using X^2 (Ng and Travis, 2008) for categorical variables. Because the distribution of age was not fit normally distribution, we used Wilcoxon rank sum test between colorectal cancer and control groups. We also calculated the incidence for gynecological cancers per 1000 person-years for both groups. Used Cox proportional hazards regression analysis to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) for gynecological cancers in the colorectal cancer group, compared with control group after controlling continuous age, comorbidity (including diabetes, hypertension, dyslipidemia, and hereditary colorectal polyposis) and multiplicative interaction variable. According to previous reports, those comorbidities were potential risk factors for gynecological cancer. We tested the possible interactions between variables. When the interaction test $p < 0.05$, we added the multiplicative interaction for adjustment in measuring HR of gynecological cancers and specific-type cancers. Because of the significant interaction between age and colorectal cancer, we assessed age-specific HR in multivariable Cox proportional hazards regression. Accounting for the competing risks of death and other types of cancer, we used the Fine and Gray model (Fine and Gray, 1999) to estimate the cumulative incidence of gynecological cancer. The identification of death events was based on hospital discharge for death or withdrawal from the NHI. Subhazard ratio (SHR) for gynecological cancer were estimated by multivariate competing-risks regression models after adjusting for

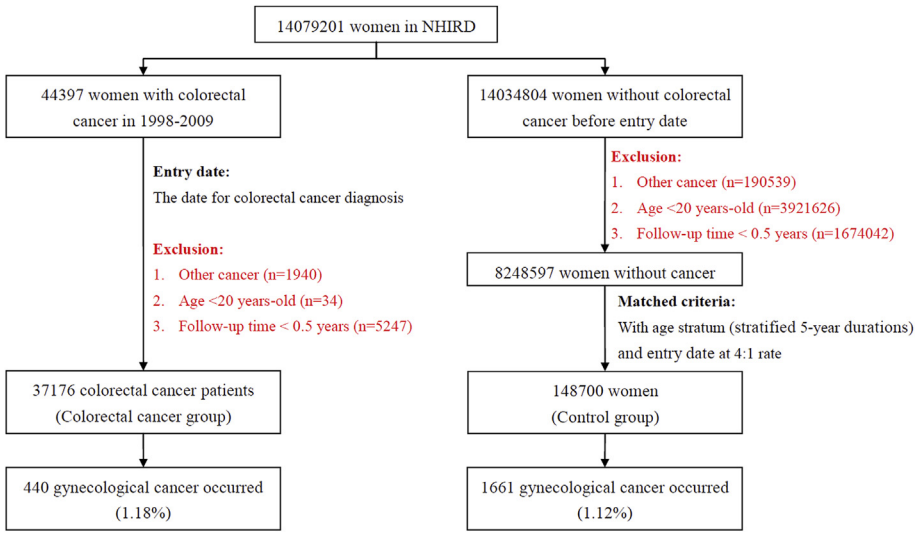

Fig. 1. Flow chart for selecting study cohorts.