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Incidences and risk factors of metachronous vulvar, vaginal, and anal cancers after cervical cancer diagnosis

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HIGHLIGHTS

- Metachronous ano-genital cancers after cervical cancer were examined.
- The risk of metachronous cancers steadily increases over time.
- Risk factors include older age, Black race, squamous histology, and radiotherapy.
- The survival of metachronous cancer is poor.

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ABSTRACT

Objective. To examine incidences and risk factors for metachronous vulvar, vaginal, and anal malignancies after a cervical cancer diagnosis.

Methods. This is a retrospective study examining data from the Surveillance, Epidemiology, and End Result Program between 1973 and 2013. Cumulative incidences of vulvar, vaginal, and anal cancers after the diagnosis of cervical cancer were assessed ($n = 79{,}050$). Multivariable analysis was performed to determine independent risk factors for these metachronous cancers.

Results. Vaginal cancer (20-year cumulative incidence, 0.57%) was the most common type of metachronous malignancy, followed by vulvar cancer (0.33%), and anal cancer (0.16%, $P < 0.001$). Median time to diagnosis was 5.4 years for vaginal cancer, 6.5 years for vulvar cancer, and 13.5 years for anal cancer. On multivariable analysis, metachronous vulvar cancer was associated with older age (hazard ratio [HR] per year 1.04, 95% confidence interval [CI] 1.02–1.05, $P < 0.001$), squamous histology (HR 2.64, 95%CI 1.38–5.05, $P = 0.003$), and radiotherapy use (HR 2.52, 95%CI 1.66–3.84, $P < 0.001$); metachronous vaginal cancer was associated with older age (HR per year 1.03, 95%CI 1.02–1.04, $P < 0.001$) and Black race (HR 1.73, 95%CI 1.20–2.48, $P = 0.003$); and metachronous anal cancer was associated with older age (HR 1.03, 95%CI 1.01–1.05, $P = 0.017$). Overall survival of metachronous cancer was poor (5-year rates: 46.3% for vulvar, 43.0% for vaginal, and 47.5% for anal cancer, respectively).

Conclusion. Although rare, the rate of ano-genital cancers continues to increase over time after a cervical cancer diagnosis. Long-term follow-up and surveillance after cervical cancer treatment is therefore reasonable to detect these metachronous malignancies, particularly in those with risk factors.

1. Introduction

Globally, cervical cancer was the most common gynecologic malignancy in 2012 [1]. While one third of women died of disease in the first five years following a diagnosis of cervical cancer, the remaining two-thirds were longer term survivors [2]. In 2012, it was estimated that there were >240,000 cervical cancer survivors in the United

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States [3]. These women face various treatment-related issues, including gastro-intestinal and urinary complications, sexual dysfunction, lymphedema, radiation toxicity, and psychosocial difficulties [4]. Yet another salient concern in this population of cervical cancer survivors is development of a metachronous secondary primary malignancy.

Generally, women with cervical cancer have various risk factors, both predating cervical cancer diagnosis and treatment-related, that increase the chance of metachronous secondary malignancy after a diagnosis of cervical cancer. First, women with cervical cancer commonly receive pelvic radiotherapy that can increase the risk of metachronous cancer in the radiated field [5]. Second, social factors, such as cigarette use, which increase the risk of malignancies in general, may predispose women to development of other types of cancers in addition to cervical cancer [6].

Third, immunosuppression, often due to human immunodeficiency virus (HIV), also imparts a higher risk of cervical cancer as well as metachronous cancers [7]. Lastly, the majority of cervical cancer is related to persistent oncogenic human papillomavirus (HPV) infection, which is implicated not only in the carcinogenesis of cervical cancer but also other ano-genital cancers [8]. For instance, 25–40% of vulvar cancers, nearly 66% of vaginal cancers, and 70–90% of anal cancers are associated with HPV infection [9–11].

Given the potential excess risks of metachronous ano-genital cancer in women with cervical cancer, population-based statistics and risk-stratification to identify at-risk populations would be beneficial in the management of women with cervical cancer. The objective of this study was to examine incidences and risk factors for metachronous vulvar, vaginal, and anal malignancies after a cervical cancer diagnosis.

2. Materials and methods

2.1. Data source and eligibility

This retrospective study utilized the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. The SEER database is a population-based tumor registry in the United States that is both publicly available and de-identified [12]. This database includes data from 1973 and covers approximately 28% of the US population. Data entry for this database is performed by personnel who are trained by the National Cancer Registrars Association, ensuring rigorous quality control [13]. The Institutional Review Board at the University of Southern California exempted this study.

The SEER18 cases between 1973 and 2013 were extracted with SEER*Stat 8.3.2 (IMS Inc., Calverton, MD, USA), generating the dataset from "Cervix Uteri" limited to malignancy and female sex. Primary cervical cancer cases with squamous, adenocarcinoma, and adenosquamous histologies were eligible for the study. Other histologic subtypes including sarcomas and metastatic tumors to the uterine cervix were excluded. The SEER*Stat 8.3.2 was also used to generate vulvar, vaginal, and anal cancer datasets for the same study period. Study identification numbers were then used to link cases in the cervical cancer dataset with those in the datasets for vulvar, vaginal, and anal cancers to detect secondary primary cancers in the same individual as described previously [14,15].

2.2. Study definition

The chronologic time sequence of the two cancer diagnoses was examined by the secondary primary cancer diagnosis (vulvar, vaginal, or anal) and the cervical cancer diagnosis dates recorded in the two datasets. If the time interval between the two diagnoses was 6 months or longer, women were considered to have a metachronous secondary primary cancer. The cutoff value of a 6-month time interval between the two cancer diagnoses for metachronous secondary primary malignancy was based on the prior studies [14–16]. Cases with time interval <6 months, diagnosis antecedent to cervical cancer, and secondary entry for vulvar, vaginal, or anal cancer were excluded from analysis.

2.3. Clinical information

Among the eligible cases for analysis, patient demographics, tumor information, treatment patterns, and survival outcome were extracted from the SEER database. Patient demographics included age, year and month at diagnosis, race/ethnicity, marital status, and registration area. Tumor information included cancer stage, histologic subtype, and tumor grade. Recorded cancer stage was based on the American Joint Committee on Cancer 7th surgical-pathological staging classification schema [17]. ICD-0-3 site/histology validation list and World Health Organization histological classification were used for grouping histologic subtypes as reported previously [18,19]. Histology types and overall survival after metachronous cancer diagnosis were also obtained for metachronous vulvar, vaginal, and anal cancer cases.

2.4. Statistical consideration

The primary objective of the analysis was to examine the cumulative incidences of metachronous vulvar, vaginal, and anal cancer in women with cervical cancer. The secondary objective of the analysis was to identify the clinico-pathological risk factors for metachronous vulvar, vaginal, and anal cancer after cervical cancer diagnosis.

In an attempt to examine patterns of risk factors for metachronous cancer, a recursive partitioning analysis was performed to construct a regression-tree model [20]. All independent covariates for metachronous cancer on multivariable analysis were entered in the final analysis, and the chi-square automatic interaction detector method was used for determining the regression-tree model. In each determined node, cumulative incidences were analyzed.

The Kaplan-Meier method was utilized to construct survival curves [21], and statistical difference between the curves was assessed with the log-rank test for univariable analysis. Cox proportional hazard regression models were used to identify independent clinico-pathological risk factors in cervical cancer for developing metachronous vulvar, vaginal, or anal cancer [22]. All the covariates with $P < 0.05$ were entered in the initial model, and the least significant covariate was removed from the model until the final model retained only the covariates with $P < 0.05$ (conditional backward method). Magnitudes of statistical significance were expressed with hazard ratios (HR) and 95% confidence intervals (CI).

All hypotheses were two-tailed, and a P-value of <0.05 was considered statistically significant. Statistical Package for Social Sciences (SPSS, version 24.0, IBM Corp, Armonk, NY, USA) was used for the analysis.

3. Results

Among 87,105 cases of cervical cancer in the database, there were 79,050 cases of squamous, adenocarcinoma, or adenosquamous cervical cancer recorded. This dataset was then linked to datasets either for vulvar cancer ($n = 22,482$), vaginal cancer ($n = 7443$), or anal cancer ($n = 16,166$).

3.1. Metachronous vulvar cancer

There were 118 women (0.15%, 95%CI 0.12–0.18) who developed metachronous vulvar cancer after cervical cancer. In a univariable analysis, women who developed metachronous vulvar cancer were older, had older year of cervical cancer diagnosis, had marital status classified as divorced/widowed/separated, and had received radiotherapy more frequently and surgery less frequently compared to those who did not develop metachronous vulvar cancer (all, $P < 0.05$) (Table 1). Cervical

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