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Follow-up of Patients with Clear-Cell Adenocarcinoma of the Vagina and Cervix

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To the Editor

Women who had prenatal exposure to diethylstilbestrol (DES) are at increased risk for clear-cell adenocarcinoma of the vagina and cervix early in life.¹ Previous studies have investigated the clinical features of this disease and survival among these patients,^{1,2} but data on their long-term survival are lacking. Women with DES-related clear-cell adenocarcinoma are aging into their 50s and 60s, but the effect of this condition during their overall life span has not been well established.

A total of 695 patients with clear-cell adenocarcinoma in the Registry for Research on Hormonal Transplacental Carcinogenesis were followed through 2014 (see the Methods section of the Supplementary Appendix, available with the full text of this letter at NEJM.org). The mean year of birth was 1955. The mean age at diagnosis of clear-cell adenocarcinoma was 22 years, and 80% of the patients received the diagnosis between the ages of 15 and 30 years. In 415 patients, evidence of prenatal DES exposure was documented.

During a median follow-up of 22.7 years, 219 patients died, yielding a probability of 20-year survival of 69%. The 5-year probability of survival differed between the patients with prenatal DES exposure (86.1%) and patients without documentation of DES exposure (81.2%), but the 20-year probability of survival was similar between the two groups (Fig. 1A). After adjustment for tumor stage, histologic type, and age, the difference in probability of survival between patients with DES exposure and those without DES exposure was significant only in the first 5 years ($P = 0.025$).

Since the epidemiologic curve was similar between the two groups,³ some of the patients with clear-cell adenocarcinoma for whom there was no documentation of DES exposure may have actually been exposed to DES in utero, and thus the true survival difference between women with DES exposure and those with idiopathic clear-cell adenocarcinoma would be larger without potential misclassification. This differential effect of DES according to time suggests that clear-cell adenocarcinoma associated with DES exposure and idiopathic clear-cell adenocarcinoma may have different tumor biologic features. Idiopathic clear-cell adenocarcinoma may be more likely to progress quickly or recur earlier, whereas clear-cell adenocarcinoma associated with DES exposure may be more likely to recur later.

This interesting phenomenon has also been observed in other estrogen-associated cancers, including breast and endometrial cancers.¹ During the first 5 to 7 years after diagnosis, patients with estrogen receptor (ER)–negative breast cancer have a worse survival than patients with ER-positive breast cancer, but the survival rates between the two groups become similar thereafter.⁴ Data from molecular studies of germline genetic mutations, tumor genomic changes, and epigenetic alterations to elucidate the underlying mechanisms for this improved behavior of estrogen-associated cancers are lacking.

We found that patients with clear-cell adenocarcinoma had increased mortality across their life span. The risk of death among women with DES-related clear-cell adenocarcinoma was 27 times higher than that in the general U.S. population of women between 10 and 34 years of age, 5 times higher between 35 and 49 years of age, and 2 times higher between 50 and 65 years of age (Fig. 1B). The excess mortality risk between the ages of 35 and 49 years is mainly due to late recurrences, whereas the excess mortality risk after 50 years of age may be due to other life-threatening health conditions in the population of women who were exposed to DES.⁵ It is therefore important to continue the surveillance of this unique cohort of patients with DES-related clear-cell adenocarcinoma to examine their health conditions late in life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Overall Survival and Risk of Death among Women with Clear-Cell Adenocarcinoma of the Cervix and Vagina

Panel A shows Kaplan–Meier estimates of the probability of survival among women with clear-cell adenocarcinoma, according to prenatal exposure to diethylstilbestrol (DES). Panel B shows the risk of death per year among women with clear-cell adenocarcinoma as compared with the risk among women in the general population in the United States. The standardized mortality ratio was calculated as the number of observed deaths in women with DES-related clear-cell adenocarcinoma divided by the expected number of deaths that would occur if the cohort had the same risk as the general population in the United States. CI denotes confidence interval.