

**Herbst A L, Ulfelder H & Poskanzer D C. Adenocarcinoma of the vagina: association of maternal stilbestrol therapy with tumor appearance in young women. *N. Engl. J. Med.* 284:878-81, 1971.**

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The sudden appearance in one area during a four-year period of eight cases of a very rare form of vaginal adenocarcinoma in eight young women led to a retrospective investigation in search of etiologic factors. Seven of the eight mothers of these patients had been treated with diethylstilbestrol during pregnancy, in contrast to none of 32 controls, indicating a statistically significant relationship between this drug and the development of the tumor. [The SC<sup>®</sup> indicates that this paper has been cited in over 760 publications since 1971.]

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September 27, 1984

"In the late 1960s, my colleagues and I at the Massachusetts General Hospital were surprised by the appearance of very rare clear-cell adenocarcinomas of the vagina in seven females 15 to 22 years of age. Previously, these tumors had been described only rarely, primarily in women over the age of 50. In collaboration with pathologist Robert E. Scully, the characteristics of the tumors were described in 1970.<sup>1</sup> The reason for their sudden appearance was not known. All of the patients had been born in New England. The mother of one of them, who had been treated by Howard Ulfelder, indicated to him that she had taken diethylstilbestrol (DES) during the pregnancy that produced her daughter. This led to the development of the study, which included an eighth case.

"David C. Poskanzer had previously conducted a number of epidemiologic studies. This study was designed collaboratively to evaluate the histories of the offspring and their families, as well as factors related to the mothers' pregnancies. With the advice of Theodore Colton of the Department of Statistics, we selected four controls for each subject. Only 34 women had to be contacted to find 32 who agreed to participate. One of the eight cancer patients had died, and her mother came to Boston to be interviewed. She, like the other mother, stated that she had taken DES during pregnancy.

"A few months after our publication, a confirmatory study was published in the *New England Journal of Medicine*.<sup>2</sup> The initial report was the first description of the association of a drug ingested during human pregnancy with the appearance of carcinoma in the offspring, which is one of the reasons it has been cited so often. The study has also been misquoted frequently with regard to the nature of the DES link as well as the magnitude of the cancer risk. For example, the article emphasized 'an association' and the rarity of the tumors in DES-exposed subjects. Subsequent investigation from a registry that was established to study these tumors, which has accessioned about 500 cases, suggested a risk of less than one per thousand exposed females.<sup>3</sup> During the dissemination of these findings to the public, misquotation of the article led to a greater degree of anxiety and apprehension than the results of the initial study warranted. Many investigators have undertaken subsequent studies on the DES-exposed population to ascertain the health status of daughters without cancer, particularly with regard to fertility and reproduction, and of sons with regard to reproductive potential and cancer risk. The health status of DES-mothers has also been studied."<sup>4</sup>

1. Herbst A L & Scully R E. Adenocarcinoma of the vagina in adolescence: a report of 7 cases, including 6 clear-cell carcinomas (so-called mesonephromas). *Cancer* 25:745-57, 1970. (Cited 210 times.)
2. Greenwald P, Barlow J J, Nasca P C & Burnett W S. Vaginal cancer after maternal treatment with synthetic estrogens. *N. Engl. J. Med.* 285:390-2, 1971. (Cited 195 times.)
3. Herbst A L, Cole P, Colton T, Robboy S J & Scully R E. Age-incidence and risk of diethylstilbestrol-related clear cell adenocarcinoma of the vagina and cervix. *Amer. J. Obstet. Gynecol.* 128:43-50, 1977. (Cited 100 times.)
4. Herbst A L & Bern H A, ed. *Developmental effects of diethylstilbestrol (DES) in pregnancy*. New York: Thieme-Stratton, 1981. 203 p.