Gynecologic Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Incidence rates and risks of diethylstilbestrol-related clear-cell adenocarcinoma of the vagina and cervix: Update after 40-year follow-up

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HIGHLIGHTS

- The rate of DES-related CCA peaked at age 19; there was a second peak at age 42.
- DES-related CCA has occurred in those as old as 55 years.
- CCA risk across birth cohorts was closely correlated with DES prescription over time.
- The cumulative risk of CCA up to the age of 50 is 1 per 750 exposed.
- There is evidence that many of the cases with negative histories were exposed.

ARTICLE INFO

Article history:
Received 26 May 2017
Received in revised form 22 June 2017
Accepted 22 June 2017
Available online xxxx

Keywords:
Diethylstilbestrol
Cervical cancer
Vaginal cancer
Epidemiology

ABSTRACT

Objective. Women exposed to diethylstilbestrol (DES) in utero are at increased risk for the development of vaginal and cervical clear cell adenocarcinoma (CCA) at younger age. It is unknown if a second peak will occur in later life, the ages when CCA developed spontaneously in the pre-DES era. The complete epidemiologic curve of CCA has not been reported, yet.

Methods. We reviewed 720 cases of CCA from the CCA registry at the University of Chicago through 2014. Incidence rates and cumulative risks for CCA were calculated based on white women born in the U.S. from 1948 through 1971.

Results. In 420 CCA cases there was documented evidence of prenatal DES exposure. 80% were among those between ages 15 and 31 but some occurred as late as age 55. A small second peak occurred around age 42. The risk of DES-related CCA was highest in the 1951–1956 birth cohort and this birth cohort effect closely correlated with DES prescriptions over time in the U.S. ($r = 0.98$, $P = 0.005$). By age 50, the cumulative risk of CCA was 1 per 750 exposed women. CCA cases without evidence of DES exposure had similar ages, year of diagnosis, and birth cohort patterns as the documented DES-exposed cases, suggesting that some negative cases were exposed. Their inclusion raises the cumulative risk of CCA to 1 per 520.

Conclusion. With the largest data available, our results confirmed the association between prenatal DES exposure and clear cell adenocarcinoma. The study also refines the risks of DES-related CCA.

1. Introduction

Diethylstilbestrol (DES), developed in 1938, was the first orally-active non-steroidal synthetic estrogen. It was used to prevent miscarriage and other pregnancy complications from 1948 to the early 1970s. Although the exact number is unknown, it has been estimated that 2–4 million pregnant women in the United States were treated with DES or a similar synthetic estrogen such as dienestrol. In 1971, the use of DES in pregnant women was reported to be strongly associated with the development of clear-cell adenocarcinoma of the vagina and cervix (CCA) in exposed daughters in their late teens or earlier twenties [1,2]. This led the Food and Drug Administration (FDA) to issue a Drug Bulletin advising physicians to stop prescribing DES to pregnant women. The Registry for Research on Hormonal Transplacental Carcinogenesis was then

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http://dx.doi.org/10.1016/j.ygyno.2017.06.028
0090-8258/

established to study the clinical/pathologic and epidemiologic aspects of these very rare tumors in DES daughters [3].

We do not know the upper age limit for the development of DES-associated CCA. It has been documented to peak at about age 19 years and it has been postulated that there may be a second increase in the occurrence of clear-cell adenocarcinoma in older DES-exposed women [4]. This is a particular concern since CCA of the vagina and cervix was more frequently diagnosed in those over age 50 years in the pre-DES era [4]. As DES-exposed daughters age, new cases of CCA may continue to occur. Multiple reports from our and other groups have described the epidemiology of DES-related CCA [2,3,5–7], but no study has reported the complete epidemiologic curve of DES-related CCA because long-term investigations are needed. A previous report on the frequency of CCA was based on registry cases that occurred through 1985 [5]. Our current analysis was undertaken to refine the current rates and risks of DES-related clear-cell adenocarcinoma using data up to 2014.

2. Methods

2.1. Data collection

In brief, the registry collects data on all cases of CCA reported to it in order to examine the clinical and epidemiological aspects of the cancer among women born after 1940 [3,5,6]. The Registry has actively sought cases of CCA in young women and efforts are made to identify all cases of the disease, regardless of maternal history of prenatal DES exposure; therefore, it also includes patients with a negative DES exposure history. Initially, letters of inquiry were sent to all Departments of Obstetrics and Gynecology at medical schools throughout the United States and Canada as well as to hospitals that specialize in cancer treatment in this country and abroad. In addition to cases received from these institutions, other cases were voluntarily reported. Pathology reports and slides, operative notes, details of radiation therapy and chemotherapy and follow-up information were sought. The epidemiologic data were obtained from the patient's family, the obstetrician, or the prenatal record, if available. In some cases this was done by the reporting physician, and in others, by registry personnel after appropriate permission had been received. Since the inception of the registry, Dr. Herbst and registry personnel worked with DES-consumer groups to identify new cases. In addition, a web page for the registry was established, all of which led to additional case accessions.

Since the HIPAA law was enacted in 2003, patients are required to report themselves to the registry or to give permission to their physicians for them to do so, and also give consent to collect information about their disease. Once a patient is reported, prenatal records, pharmacy prescriptions, and hospital records are examined when they are available. Prenatal histories of medications can be divided into four categories: verified DES exposure, positive for use of another hormone such as progesterone and steroidal estrogens or for an unidentified medication, negative for use of hormones or other medications, and unknown maternal medication history. Clinical data are obtained from the patient's physician and patients are also contacted intermittently to report their health status and the development of any new malignancies, recurrent clear-cell adenocarcinoma, and other serious health developments. The study was approved by the Institutional Review Broad at the University of Chicago.

2.2. Incidence rates and risks

The age-specific incidence rates of DES-related CCA were calculated with the numerator being CCA cases with confirmed (documented) in utero DES exposure, white race (almost all CCA cases), and those who were born in the United States in 1948 through 1971. The birth cohort of 1948 was the oldest group to be included in the analysis because 1947 was the first year in which DES was commonly used to prevent miscarriages and other pregnancy problems. There were 10 CCA cases born in 1948 in the registry, an occurrence which is higher than the 8 cases born in the years of 1945–1947. The birth cohort of 1971 is the youngest to be included in the analysis because it is the year in which the FDA removed "prevention of miscarriage" as an indication for DES use and added pregnancy as a contraindication. No clear-cell adenocarcinoma case in the registry with documented DES exposure was born after 1971. Three-year birth cohorts (1948–1950 through 1969–1971) were formed because the number of cases was very small in a single-year birth cohort. The denominators of the incidence rates were the age- and calendar year-specific population of white females born in the United States between 1948 and 1971. These estimates were taken from the United States decennial censuses and intercensal estimates (www.census.gov). After age-specific incidence rates were calculated, we also calculated the cumulative rates of developing clear-cell adenocarcinoma from birth to a specified age. They are the summation of single-year age-specific incidence rates up to the specified age. The cumulative rates can be interpreted as cumulative risks for a rare disease like clear-cell adenocarcinoma [8].

We also estimated the rates and risks of DES-related clear-cell adenocarcinoma among women who were exposed prenatally to DES. The method of estimating the relative extent of each cohort exposed to DES was described in previous reports [5,9]. An exposure index was calculated for each birth cohort as the number of 25 mg tablets of DES sold by one pharmaceutical company in the United States (primarily used for pregnancy support) each year divided by the number of live births in a subsequent year [9]. This exposure index serves as a surrogate of relative exposure in the population. The probability that a woman in the 1960–1962 birth cohort was exposed to in utero DES has been estimated to be 7.3% [10]. The probabilities of exposure to DES in other birth cohorts were estimated by multiplying the relative exposure index and the probability of exposure in the 1960–1962 cohort. Then, the number of women exposed to DES in each cohort was calculated as the product of the probability of DES exposure and the population sizes from US census described above.

Because some of the CCA cases who did not have documented DES exposure may have been exposed, the rate calculation based on CCA cases with clear documentation of prenatal DES exposure may underestimate the true rate. As a sensitivity analysis, we also conducted a rate calculation using all white CCA cases who were born in the US between 1948 and 1971 as the numerator.

2.3. Statistical model of age at diagnosis

To test whether there is a second peak of CCA occurrence in older DES-exposed women, we modeled the age at CCA diagnosis using a finite mixture distribution model [11]. In particular, we fit a mixture model of 2-component log-normal distributions to age at diagnosis and compared to one-component model, which is equivalent to one-peak distribution. A log likelihood ratio test was performed for model comparison. All the analyses were conducted in Stata 14 (StataCorp LP, College Station, TX) and *fmm* module in Stata was used to fit mixture models.

3. Results

3.1. Total cases

A total of 720 cases of clear-cell adenocarcinoma were recorded in the registry through December 31, 2014. Of these cases, 400 patients had vaginal cancer, 182 had cervical cancer, and 138 had a cancer involving both the vagina and cervix. In 421 cases (58%), there was documentation that the mother had been treated with DES. In 71 cases (10%), the mother had received some other hormone or an unidentified medication. In 169 cases (23%), no exposure to hormones or medications was documented. In the remaining 59 cases (8%), in utero medication exposure was unknown. Table 1 presents the demographic

Please cite this article as: D. Huo, et al., Incidence rates and risks of diethylstilbestrol-related clear-cell adenocarcinoma of the vagina and cervix: Update after 40-year f..., Gynecol Oncol (2016), http://dx.doi.org/10.1016/j.ygyno.2017.06.028