Gynecologic Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Risk of cervical intra-epithelial neoplasia and invasive cancer of the cervix in DES daughters

J. Verloop [a], F.E. van Leeuwen [a], Th.J.M. Helmerhorst [b], I.M.C.M. de Kok [c], E.J.M. van Erp [d], H.H. van Boven [e], M.A. Rookus [a,*]

[a] Department of Epidemiology, Netherlands Cancer Institute, Amsterdam, The Netherlands
[b] Department of Obstetrics and Gynaecology, Erasmus MC, University Hospital Rotterdam, The Netherlands
[c] Department of Public Health, Erasmus MC, The Netherlands
[d] De Praktijk, Utrecht, The Netherlands
[e] Department of Pathology, Netherlands Cancer Institute, Amsterdam, The Netherlands

HIGHLIGHTS

- Information on CIN was based on the nationwide pathology registry.
- No increased risk for CIN2+ was found among DES daughters.
- DES daughters with DES-related malformations had higher rates of CIN1 probably due to screening.

ARTICLE INFO

Article history:
Received 22 August 2016
Received in revised form 23 November 2016
Accepted 29 November 2016
Available online xxxx

Keywords:
Diethylstilbestrol
Squamous neoplasia
Cervical dysplasia
Cervix
Pap smear screening

ABSTRACT

Objective. Women exposed to diethylstilbestrol in utero (DES) have an increased risk of clear cell adenocarcinoma (CCA) of the vagina and cervix, while their risk of non-CCA invasive cervical cancer is still unclear.

Methods. We studied the risk of pre-cancerous (CIN) lesions and non-CCA invasive cervical cancer in a prospective cohort of 12,182 women with self-reported DES exposure followed from 2000 till 2008. We took screening behavior carefully into account. Incidence was obtained through linkage with the Netherlands Nationwide Pathology database (PALGA). General population data were also derived from PALGA.

Results. The incidence of CIN1 was increased (Standardized Incidence Ratio (SIR) = 2.8, 95% Confidence Interval (CI) = 2.3 to 3.4), but no increased risk was observed for CIN2+ (CIN2, CIN3 or invasive cancer) compared to the screened general population (SIR = 1.1, 95% CI = 0.95 to1.4). Women with DES-related malformations had increased risks of both CIN1 and CIN2+ (SIR = 4.1, 95%CI = 3.0 to 5.3 and SIR = 1.5, 95%CI = 1.1 to 2.0, respectively). For CIN2+, this risk increase was largely restricted to women with malformations who were more intensively screened.

Conclusions. An increased risk of CIN1 among DES daughters was observed, especially in women with DES-related malformations, probably mainly due to screening. The risk of CIN2+ (including cancer) was not increased. However, among DES daughters with DES-related malformations a true small risk increase for non-CCA cervical cancer cannot be excluded.

1. Introduction

In the late 1940s to the early 1970s several millions of pregnant women worldwide received Diethylstilbestrol (DES) in order to prevent miscarriages and other pregnancy complications [1–4]. Next to high risk of clear cell adenocarcinoma of the vagina and cervix (CCA), the well-established adverse health effects in the female offspring (DES daughters) include several reproductive tract abnormalities, among which are the presence of glandular tissue (adenosis) and metaplastic squamous epithelium in the vagina and ectocervix. It has been speculated that these epithelial changes might increase the risk of cancer, not only adenocarcinoma, but also squamous cell cancer, and precancerous lesions [5–8]. A two-fold risk of cervical dysplasia (CIN2+) was observed in the National Cancer Institute's DES Combined Cohort Follow-up Study (NCI DES study), with a 74% increased risk among DES daughters who had vaginal epithelial changes [7,8]. For invasive

* Corresponding author at: Department of Epidemiology, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands.
E-mail address: m.rookus@nki.nl (M.A. Rookus).

http://dx.doi.org/10.1016/j.ygyno.2016.11.048

squamous cell cervical cancer findings were inconclusive [9]. In a previous report of our Dutch DES cohort a (non-statistically significant) decreased risk of invasive squamous cell cervical cancer was found [10].

In this report we examined the risk of cervical intra-epithelial lesions (CIN) and cervical cancer in a large cohort of Dutch DES-daughters, compared to the screened general population. A unique feature of this study is that all outcomes and reference data were obtained from the Netherlands nationwide pathology database (PALGA), which enabled us to account for screening behavior.

2. Patients and methods

The DES-net project is a nationwide retrospective cohort study with prospective follow-up among DES daughters in the Netherlands. DES daughters were identified through the registry of the Netherlands DES Center that was established in 1992 in order to deal with future health claims. Documented DES exposure at time of registration was not required. In the period March 2000–December 2004 DES daughters were sent a 16-page self-administered questionnaire about risk factors for hormone-related cancers and medical history (response 63%, supplementary Fig. 1). In addition to the questionnaire, women granted permission to abstract data from their medical records by means of a written informed consent. Furthermore, women provided us, if available, with a copy of the medical file of their mothers in which DES exposure in utero was confirmed.

3. Assessment of outcome and screening history

Detailed information on CIN, invasive cervical cancer and screening history was retrieved from PALGA [11]. PALGA is a nationwide database of excerpts of all histopathology and cytopathology reports made since 1989. The PALGA Surveillance Committee granted us permission to link all study subjects with PALGA (both responders and non-responders to the questionnaire, but refusers (6%) excluded) under strict privacy procedures. The study was approved by the Institutional Review Board of the Netherlands Cancer Institute.

All CINs and cancer were coded according to the systemized nomenclature of medicine (SNOMED). For each woman the first occurrence of the highest grade of CIN was used in the analysis (supplementary Table 1). CIN1 was defined as mild dysplasia, CIN2 as moderate dysplasia, CIN3 as severe dysplasia or carcinoma in situ and cervical cancer as invasive cervical squamous cell carcinoma and non-CCA adenocarcinoma. CIN2 + was defined as a combination of CIN2, CIN3 and invasive cancer. For each woman the number of episodes, as a proxy for the number of screening rounds, was calculated. By definition, a screening episode started with a primary smear, if necessary followed by secondary smears in case of an abnormal smear or a smear of inadequate quality. An episode ended when follow-up was complete according to the Dutch guidelines (i.e. the dates of the third consecutive negative smears after a primary smear with high grade squamous cell intra-epithelial lesion (HSIL) smear, the second consecutive negative smears after a primary smear with low grade squamous cell intra-epithelial lesion (LSIL), the one consecutive adequate smear after a primary smear of inadequate quality within 6 months, or at the date 4 years after the primary smear when no (adequate) follow-up smears were done. Thus, by definition, post-diagnostic follow-up smears were attributed to the same episode as the diagnosed lesion.

4. Covariates

Questionnaire data on DES-related reproductive tract abnormalities (including adenosis, squamous cell metaplasia, transverse vaginal ridges, cockscomb, cervical collars, hoods, pseudo-polyps, hypoplastic cervix, uterine cavum malformations and tubal malformations) were verified by medical file. The term vaginal/cervical epithelial changes (VCEC) is used to refer to adenosis or squamous cell metaplasia of both the vagina and the ecto-cervix (enlarged ectropion). Other covariates (educational level, indication for maternal DES usage, age at first gynaecological DES examination, and number of smears and colposcopies during five years preceding the questionnaire) were based on self-report. Vital status was obtained by linkage with the Netherlands Office of Death Registry (CBG) and updated till October 2007.

5. Verification of DES exposure

Documented DES exposure was available for a minority of subjects. Mothers' medical records were hard to trace as archives of hospitals and general practitioners had been destroyed. For a subgroup of participants ($n = 115$) we verified self-reported DES exposure with medical records in four hospitals where all records had been kept [10]. For 76% of the women DES exposure was confirmed, in 3% a medicine different from DES was recorded and in 21% no DES was mentioned in the hospital medical file, while prescription by general practitioner could not be excluded. Because the agreement between self-report and verified DES-exposure was acceptable, we included all women in the analyses, irrespective of whether DES exposure was medically verified.

6. Statistical analysis

Follow-up started on January 1st 2000, at age 29 years, whichever was last. We excluded women younger than age 29 because the Dutch general population screening program is restricted to women aged 30–60 years, and women are invited in the year they become 30 years. Follow-up ended at 30th November 2008, the date of first occurrence of intra-epithelial cervical neoplasia (CIN) or cervical cancer, death, date of uterus extirpation/cervix amputation, date of the 65th anniversary, whichever came first. After exclusion of ineligible women ($n = 287$, supplementary Fig. 1), 11,895 women (100,287 person-years) were left for analyses.

Standardized Incidence Ratios (SIRs) were calculated by comparing the number of observed cases with CIN and invasive cervical cancer in our study with age-, sex- and calendar period–specific numbers from PALGA [12,13]. The number of women at risk in the general population was obtained from Statistics Netherlands (www.cbs.nl) and adjusted for women without an uterus (from the Dutch Hospital Discharge database (LMR), based on 5-year age categories (30–64)). To calculate the total number of screened women at risk in the general population we additionally applied 5-year coverage rates per five year age category from the year 2005 [14] (supplementary, Table 2). 95% confidence intervals (CI) were calculated assuming a Poisson distribution [15].

Because it is generally known that first screens have higher detecting rates than following tests, we excluded prevalent lesions, detected during the first screening episode, both in the general population as the study population. In order to achieve this for the latter population, analyses were restricted to participants who reported to have had a smear during the five years preceding the questionnaire. Furthermore, we calculated SIRs for women stratified according to the number of episodes, the presence of DES-related malformations and attained age. Additionally, we examined which type of examination (biopsy or cytology) and which outcome directly preceded the histological diagnosis of CIN.

We used the Kaplan-Meier method to compare the cumulative incidence of CIN lesions among subgroups of women. Furthermore, Cox regression analysis was performed to calculate hazard ratios (HR) in order to quantify the effect of different covariates on the risk of CIN within the exposed cohort, with adjustment for the other covariates. Both in the Kaplan-Meier and the Cox regression model, age was used as the time metric. All analyses were conducted using STATA release 11 SE.

Please cite this article as: J. Verloop, et al., Risk of cervical intra-epithelial neoplasia and invasive cancer of the cervix in DES daughters, Gynecol Oncol (2016), http://dx.doi.org/10.1016/j.ygyno.2016.11.048