Clear Cell Adenocarcinoma of the Vagina and Cervix

An Update of the Central Netherlands Registry Showing Twin Age Incidence Peaks

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BACKGROUND. The objective of this study was to update the registry of women in the Netherlands with clear cell adenocarcinoma (CCAC) of the cervix or vagina with or without intrauterine exposure to diethylstilbestrol (DES).

METHODS. From a nationwide search in PALGA, the automated pathology registry in the Netherlands, data were gathered on women with CCAC born after 1947. Information obtained from the clinical files of the patients included reported exposure to DES, patterns of complaints previous to diagnosis, the current status of the patients, and the results of cytopathologic examinations previous to histopathologic diagnosis. After review of the histopathologic slides, the specific pathologic characteristics of CCAC were determined. The age distribution of women born after 1947 was compared with that of women born before 1947.

RESULTS. Information about possible exposure to DES during pregnancy was available for 73 of 88 women with CCAC born after 1947. Exposure to DES was reported for 47 (64%) of these women. The DES medication was most often reported as having started before the 18th week of pregnancy. Cytopathologic examination was informative in 81% of the cases of CCAC of the cervix, but only in 41% of the cases of CCAC of the vagina. Most patients had Stage I or II tumors at diagnosis. Tumor Stage III and IV and a high grade of nuclear atypia were related to unfavorable outcome. The age distribution of all patients with CCAC showed two distinct peaks: one at young age, (a mean age of 26 years), and one at older age (a mean age of 71 years). This bimodal age distribution still applied when the cases in which DES exposure was reported had been excluded.

CONCLUSIONS. Despite the fact that DES has not been prescribed to pregnant women in the Netherlands in the last 20 years, CCAC is still relevant in our times. It is important to stay alert and periodically to update and evaluate the data of this registry, including data on women born outside the DES exposure period. The bimodal age distribution in this study of women without intrauterine exposure to DES suggests a carcinogenesis-promoting role of menarche and menopause and/or the existence of a subpopulation with genetic risk factors or exogenous risk factors other than exposure to DES. Postmenopausal observation of women exposed to DES must be encouraged for clinical reasons and may help facilitate differentiation between these two hypotheses. If these risk factors of CCAC were better documented and their interrelationships better defined, CCAC could become an important model of multistep carcinogenesis in tissues sensitive to sex hormones. *Cancer* **1997;79:2229–36.** © *1997 American Cancer Society.*

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Since a publication in 1971 by Herbst et al, several studies have linked the occurrence of vaginal clear cell adenocarcinoma (CCAC) in young women with intrauterine exposure to the synthetic nonsteroid estrogenic hormone Diethylstilbestrol (DES).[1] DES has been prescribed in several countries to pregnant women as a preventive ther-

apy against abortion.[2] Based on crude estimates of exposure and sales, it has been estimated that in the U. S. 1 to 4 million women have used DES during pregnancy.[3] Melnick et al estimated that the chance of developing a CCAC is 1 in 1000 for DES-exposed women.[4] Until 1989, the central American voluntary registry had registered 547 patients with CCAC; in 60% of those cases, the mother was reported as having used DES during pregnancy.[5] However, the absence of cases of CCAC in prospective cohort studies, its occurrence at an apparently similar rate in Norway (a country in which DES was not available[6]), and biases in the studies incriminating DES have led other epidemiologists to question the relation between DES and CCAC.[7] In the Netherlands, DES was prescribed from 1947 until 1975.[8] Previous publications have examined the occurrence of CCAC in the Netherlands.[9,10] Until January 1, 1982 in the Netherlands, 21 patients were known to have CCAC.[9] Of these, 16 mothers were reported as having used DES (76%). In 1991 the results of a study of 55 Dutch CCAC patients diagnosed before July 1, 1988 were published; DES exposure was reported in 63% of the patients with data on maternal history.[10] The total consumption of DES in the Netherlands cannot be traced. This can be attributed to the multitude of companies distributing DES in the Netherlands; moreover, pharmacists work with bulk products rather than with individual factory packaging. The Dutch DES Action and Information Center has estimated that 189,000 to 378,000 women would have been exposed to DES during their mother's pregnancy.[8]

The objective of the current descriptive study was to update, through June 1993, the epidemiologic, clinical, and pathologic data of women with CCAC of the vagina or cervix. Attention was given to the incidence of the tumor, DES exposure, the significance of cytopathologic examination for the early detection of this disease, signs and symptoms discovered previous to the diagnosis, prognostic parameters, and the age of the patients. In addition, the nationwide completeness of pathologic records since 1988 in the Netherlands also allowed the registration of cases of CCAC in women born before 1947, before DES was prescribed in the Netherlands.

PATIENTS AND METHODS

For the registry update, an inventory was made of all patients with a diagnosis of CCAC of the cervix and/or vagina who were born after 1947. For this purpose, a nationwide search was performed in the automated pathology archive, PALGA. Since 1988, all Departments of Pathology in the Netherlands have been connected to the PALGA computer network. The results of the nationwide search indicated in which Departments of Pathology the diagnoses of CCAC of the cervix and/or vagina had been made. The involved departments were asked for a copy of the report of the histopathologic examination. If the patient was already known from a previous evaluation, the new information was added to the known data. If a patient was born after 1947 and had not yet been registered at the Central Netherlands Registry (CNR) for CCAC, the patient was registered after transfer of a signed declaration of approval of scientific research. The CNR received declarations from some patients via the Dutch DES Action and Information Center, and for the remaining patients via their gynecologists.

The relevant histologic slides of the selected patients were reviewed by two pathologists (A.H. and J.B.). If the diagnosis of CCAC was confirmed, a standard questionnaire requesting the following data was sent by the researchers (A.H., M.L., O.S.) to the patient's doctors, who were asked to consult their clinical files: the year of diagnosis, presence or absence of intrauterine DES exposure, reason for DES prescription, localization and stage of the tumor, treatment for CCAC, patient's use of contraception, signs and symptoms before the diagnosis, and current status of the patients. The following data of the patients who were already known at the CNR before 1988 were recorded: current status, presence of recurrence or metastasis, supplementary therapy, date of last examination, and more recent information concerning intrauterine DES exposure.

At histopathologic review, the following characteristics were registered: tumor localization within the cervix or vagina, size of the tumor, mitotic activity, grade of nuclear atypia, and histologic growth pattern. The mitotic activity was defined as the number of mitoses per 10 high-power fields (HPF = objective X40). The grade of nuclear atypia was determined according the criteria of Christopherson et al,[11] based on the shape and size of the nuclei, the presence and shape of nucleoli, and the chromatin pattern. The growth pattern of CCAC in this study was classified as: predominantly tubulocystic, solid, papillary, or mixed. Based on the PALGA data of the selected women, the results of cytopathologic examination of vagina and/or cervix (performed up to 2 years before the histopathologic diagnosis) were also recorded.

Because DES was not prescribed in the Netherlands until 1947,[8] and until the time of study the CNR had focused on DES-associated pathology, no patients registered in the CNR had been born before 1947. However, for this study cases of patients born before 1947 who had a diagnosis of CCAC after 1988 could be registered because by that time the PALGA was completely nationwide.

RESULTS

Incidence of CCAC in Women Born after 1947

As a result of the nationwide search in PALGA, it appeared that since the last evaluation of the CNR in 1988 CCAC had been diagnosed in 27 patients born after 1947. One patient from Suriname, who had stayed in the Netherlands for 3 months for treatment of her CCAC, was excluded from the current evaluation. Another seven patients were included, two patients for whom the CNR did not have all data available in 1988, and two new patients who had been reported by their gynecologists to the CNR during the current evaluation. Histopathologic review of the slides of three patients who were not known at PALGA but who were known at the DES Action and Information Center confirmed the presence of CCAC. Together with the 55 patients who were known in 1988, the registry as of May 1993 included data from 88 women with CCAC. All tumors of these 88 patients had been diagnosed between 1969 and 1993. The highest incidence (ten women) occurred in 1988. Thereafter, the incidence appeared to decrease, but more time is necessary to elapse before this can be ascertained. The oldest patient was born in 1947, and the youngest in 1973. The year in which the most women (n = 10) with CCAC were born was 1960.

DES Exposure

Maternal information of intrauterine DES exposure could be obtained from 73 of 88 patients born after 1947. This information was obtained from the medical records or in some cases from questionnaires returned by the gynecologists (n = 64) or the general practitioners (n = 7) of the CCAC patients. In two cases, statements of DES exposure were received through declarations of the patients themselves to the DES Action and Information Center. In 47 of the 73 patients with information on maternal history (64%), it was stated that they had been exposed to DES. In 20 patients (27%) no report of exposure to DES was given. For 6 patients (8%) it was not known whether the mother had used DES during the pregnancy. A reason for DES prescription was given in 25 of the 47 women reported as having been exposed to DES. The most frequent reason (n = 15) was that the mother had had difficulties in a previous pregnancy, such as abortion or threatened abortion and abnormal blood loss.

Of the 47 reportedly DES-exposed patients, the majority (29 patients; 62%) had carcinoma of the vagina (possibly with extension to the ectocervix, but not to the endocervix); 18 (38%) patients had a CCAC of the cervix. Of the 20 patients with a negative DES history, approximately two-thirds (14 patients; 70%) had a CCAC of the cervix.

Data on the point in the pregnancy at which DES medication was reportedly started could be obtained from 30 patients. In 21 patients DES was reported as having been used before the 18th week, in 8 patients it was believed to be prescribed before the 18th week, and in 1 patient it was prescribed after the 18th week of pregnancy.

Cytologic Examination

Of the group of 88 young patients with CCAC, cytologic examination had been performed in 49% (43 patients) within 2 years before the histologic diagnosis. Of these 43 patients, 28 women (65%) had a "positive" cytologic diagnosis ("suspected malignant" or "malignant") and 15 patients (35%) had a "negative" cytologic diagnosis ("no abnormalities" or "atypia"). The percentage of detected carcinomas of the cervix was higher than that of the vagina. Twenty-one of the 26 patients with a cervical carcinoma (81%) and 7 of the 17 patients with a CCAC of the vagina (41%) had a "positive" cytologic diagnosis.

Signs and Symptoms

Of the 88 patients born after 1947, 57 had reported vaginal blood loss before the diagnosis of CCAC was made. Eleven patients reported dyspareunia. Seven patients (8%) had their CCAC diagnosed during a regular examination because of known intrauterine DES exposure. In 6 patients (7%) no symptoms were mentioned. The duration of the symptoms was < 6 months in 42 patients and > 6 months in 30 patients. There was no clear relation between the duration of symptoms and mortality of CCAC.

Clinical Status

Of the 88 women with CCAC of the vagina or cervix, 18 (20%) had died of disease before May 1, 1993. Nine patients who had died of the tumor had a CCAC of the cervix and nine a CCAC of the vagina. Eight of the 12 dead patients (67%) with known maternal history of DES exposure had been exposed to DES. All 18 patients died within 5 years of the initial diagnosis (range, 11–53 months). Nine of the 18 dead patients had remaining tumor since the initial diagnosis; three had metastases. The remaining nine patients had developed a local recurrence and/or metastases. The metastases were usually pulmonary or in the lymph nodes (inguinal, paraaortic, and supraclavicular). All local recurrences had been diagnosed within 3 years after the initial diagnosis (range, 5–30 months). At last follow-up, 61 patients were alive without signs of tumor. Two of these patients were without any signs of malignancy after surgical treatment for a local recurrence (follow-up periods after treatment of the recurrence were 51

TABLE 1
Relation between Clinical Status of the Patients and Tumor Stage

Stage	Total	DOD	≤ 5 survivors	> 5 survivors	Status unknown
I	36 (100%)	4 (11%)	11 (31%)	20 (56%)	1 (3%)
II	41 (100%)	9 (22%)	6 (15%)	25 (61%)	1 (2%)
III	6 (100%)	2 (33%)	0	4 (67%)	0 (0%)
IV	4 (100%)	3 (75%)	0	0	1 (25%)
Total	87	18	17	49	3

DOD: dead of disease; > 5 survivors: patients alive > 5 years after initial diagnosis; ≤ 5 survivors: patients alive with a follow-up of < 5 years.

months and 62 months, respectively), and 1 patient was alive without signs of malignancy after treatment of a local recurrence in 1978 and treatment of a solitary metastasis in the left lung hilus in 1980. Three patients were alive with recurrence or metastasis (range of follow-up period, 12–48 months), and 2 patients were alive without complete follow-up data. No follow-up data were available for four patients.

Tumor Characteristics and Prognostic Parameters

Using the criteria of the International Federation of Gynecology and Obstetrics,[12] 41 tumors (47%) were classified as CCAC of the vagina and 47 (53%) as CCAC of the cervix. If the tumor involved the anatomic endocervix but had a predominantly vaginal localization, it was still considered to be a CCAC of the cervix. The tumor was localized in the upper one-third of the vagina and/or cervix in 74 patients. Tables 1 and 2 show the relation between clinical status and tumor characteristics. The percentage of patients who died correlated with higher stages (Table 1). There was no clear difference in tumor stage between patients with or without DES exposure. No data on survival were known for three patients. For two patients, a complete revision of the histologic slides was not possible. Tables 1 and 2 show that the following characteristics coincided with an unfavorable outcome: Stage III or IV, a tumor of > 40 mm in greatest dimension, a solid histologic growth pattern, a high number of mitoses (> 10 per 10 HPF), and Grade 3 nuclear atypia. In an earlier report by the CNR, a classification criterion had been mentioned for the prediction of disease outcome in CCAC patients that was based on grade of nuclear atypia (NA) and tumor stage (STA).[10] The group of patients known to be alive was divided into 2 subgroups: patients alive > 5 years after the diagnosis ("> 5 survivors") and those who were alive with a follow-up period of < 5 years ("< 5 survivors"). The subgroup of < 5 survivors was comprised of 21 patients. On the basis of the classification criterion of 1988, 2 of these patients had an unfavorable prognosis and 19 had a favorable prognosis. In the current study follow-up was not available for 1 of these 19 patients with a favorable prognosis. At last follow-up, the remaining 18 patients were still alive after the diagnosis. Two patients were alive with a local recurrence, one patient was alive with lung metastasis, and two patients were alive without signs of malignancy after treatment for local recurrence. Of the two patients with an unfavorable prognosis (1% and 36%, respectively, chance of surviving > 5 years), the first patient with CCAC of the vagina (NA = 3, STA = IV) died 26 months after the initial diagnosis. The other patient with CCAC of the vagina (NA3, STA2) was still alive > 5 years after the initial diagnosis without signs of malignancy.

Age Distribution of CCAC Patients Born after 1947

The age at diagnosis of the 88 CCAC patients born after 1947 is shown in Figure 1. The youngest patient was age 8 years and the oldest 37 years. The mean age was 23.6 years. The age of DES-exposed woman ranged from 14 years to 37 years with a mean age of 21.3 years. The youngest patient who had not been exposed to DES was age 18 years at diagnosis and the oldest was age 37 years. The mean age in this patient group was 26.1 years.

Age Distribution of All CCAC Patients (Including Those Born before 1947)

Figure 2 shows the age distribution of 64 patients diagnosed with CCAC between 1988 and 1993, regardless of the year of birth (before or after 1947). The figure shows two clearly separated prominent peaks. The first peak contains data of 30 young women with ages ranging from 17 to 37 years; the mean age was 26 years. The second peak contains data from 34 older women (all born before 1947) and ranges in age from 44 to 88 years; the mean age was 71 years. The first peak includes all DES daughters. In Figure 3, the ages of the same group of women are shown, excluding women with a positive

TABLE 2
Several Histopathologic Parameters in Relation to Clinical Status of the Patient

	Total	DOD	≤ 5 survivors	> 5 survivors	Lost to follow-up
Tumor size (mm)					
< 40	51 (100%)	4 (8%)	12 (24%)	34 (67%)	1 (2%)
> 40	27 (100%)	12 (44%)	4 (15%)	9 (33%)	2 (7%)
Unknown	10 (100%)	2 (20%)	1 (10%)	6 (60%)	1 (10%)
Growth pattern					
Tubulocystic	51 (100%)	6 (12%)	11 (22%)	33 (65%)	1 (2%)
Solid	16 (100%)	7 (44%)	1 (6%)	6 (38%)	2 (13%)
Papillary	2 (100%)	1 (50%)	—	1 (50%)	—
Mixed	17 (100%)	4 (24%)	4 (24%)	8 (47%)	1 (6%)
Unknown	2 (100%)	—	1 (50%)	1 (50%)	—
Mitoses/10 HPF					
< 10	58 (100%)	7 (12%)	12 (21%)	36 (62%)	3 (5%)
> 10	24 (100%)	10 (42%)	3 (13%)	10 (42%)	1 (4%)
Unknown	6 (100%)	1 (17%)	2 (33%)	3 (50%)	—
Nuclear atypia					
Grade 1	5 (100%)	1 (20%)	—	4 (80%)	—
Grade 2	47 (100%)	3 (6%)	14 (30%)	26 (55%)	4 (9%)
Grade 3	30 (100%)	13 (43%)	2 (7%)	15 (50%)	—
Unknown	6 (100%)	1 (17%)	1 (17%)	4 (67%)	—
Total	88	18	17	49	4

DOD: dead of disease; HPF: high-power fields.

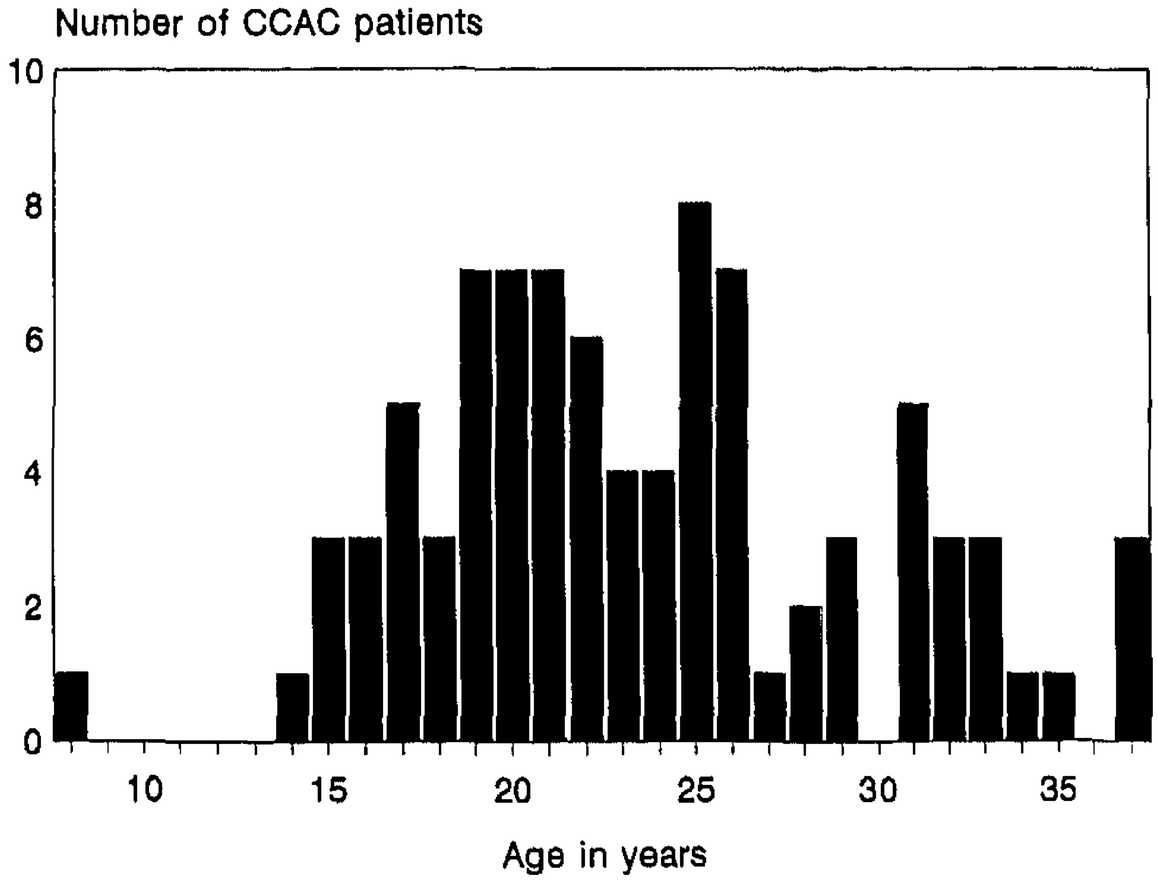

FIGURE 1. Age at diagnosis of CCAC patients born after 1947 (n = 88). CCAC: clear cell adenocarcinoma.

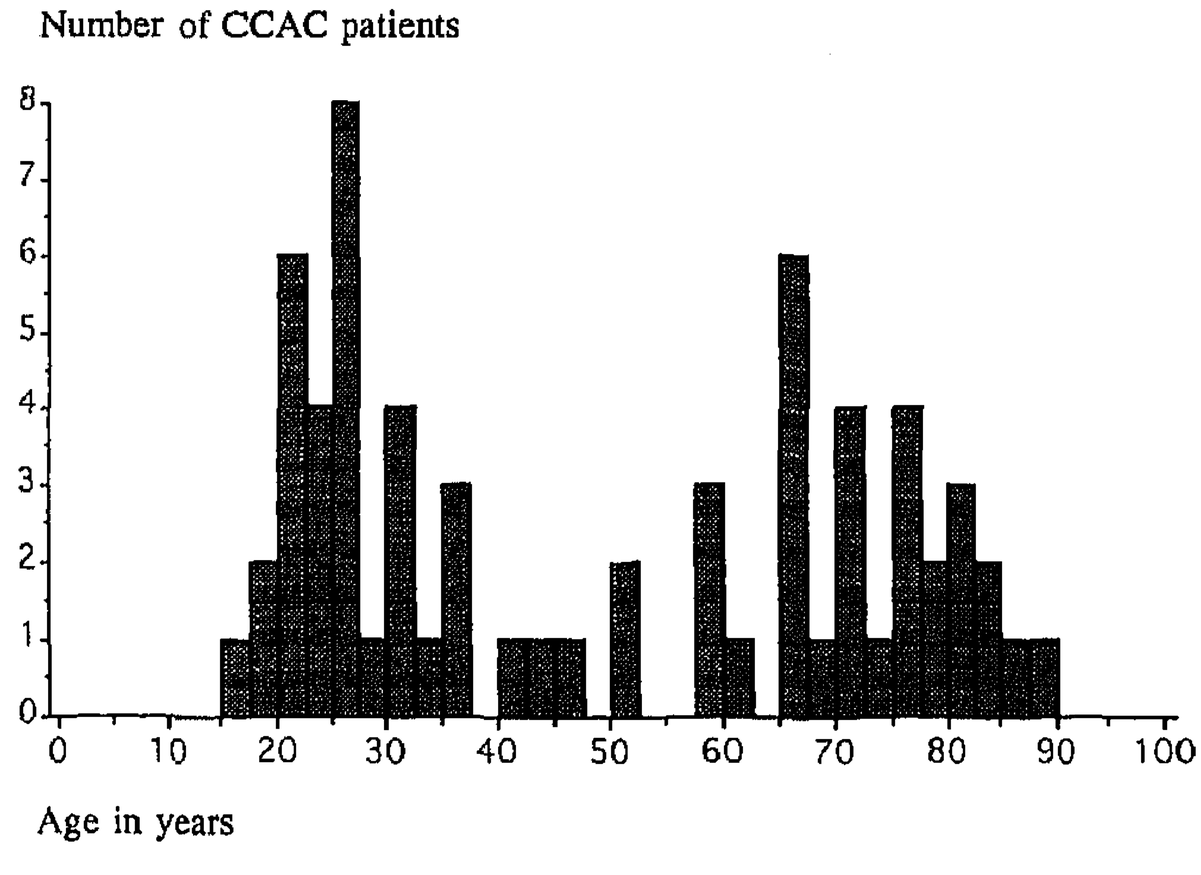

FIGURE 2. Age distribution of all patients with clear cell adenocarcinoma (CCAC) diagnosed since 1988, regardless of whether they were born before or after 1947 (n = 64).

DES history. In Figure 4, the women with an uncertain DES history (n = 5) are excluded. These figures also show a bimodal distribution; a peak is visible at young age. No transformation allows the distribution to be normal, and it contains two populations by maximal likelihood statistical analysis. Approximately two-thirds of the 34 older women had CCAC of the cervix (22 patients) and one-third had CCAC of the vagina (12 patients). The same ratio applied for the younger women who had not been exposed to DES or whose DES history was unknown. Two-thirds of the young women who had been exposed to DES had a CCAC of the vagina (11 patients), and one-third of the patients had CCAC of the cervix (5 patients).

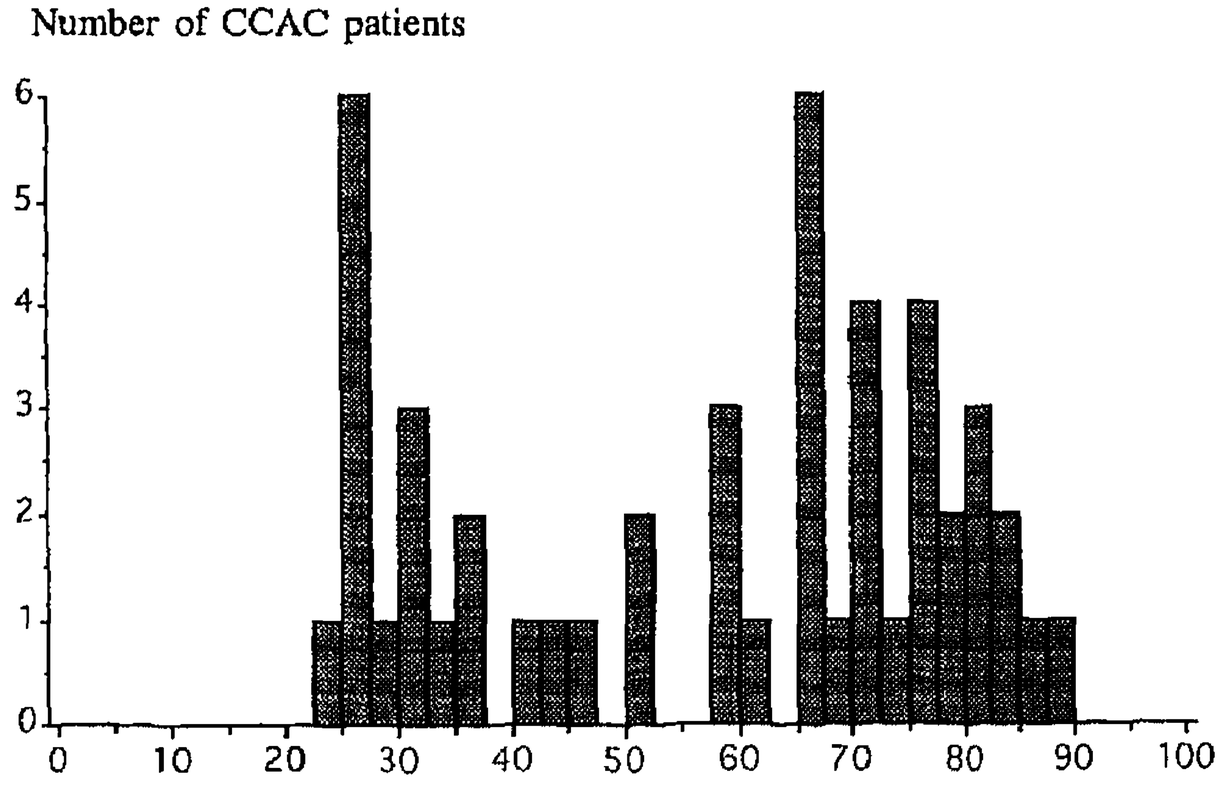

FIGURE 3. Age of all patients with clear cell adenocarcinoma (CCAC) diagnosed since 1988, excluding women reported as having been exposed to diethylstilbestrol (n = 48).

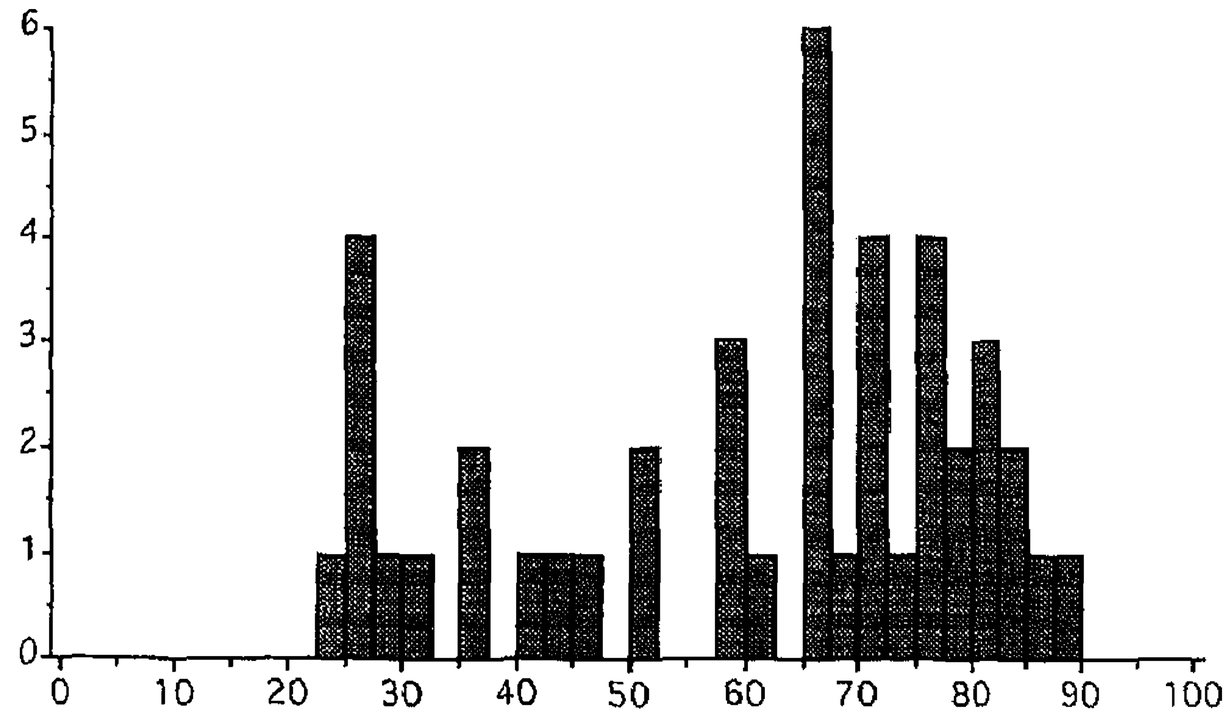

FIGURE 4. Age of the patients with clear cell adenocarcinoma (CCAC) diagnosed since 1988, as in Figure 3, but excluding those patients with an uncertain history of diethylstilbestrol exposure (n = 43).

DISCUSSION

In this overview the epidemiologic, clinical, and histopathologic characteristics have been described in a group of 88 Dutch women born after January 1947 with a CCAC of the cervix or vagina diagnosed before May 1993. The increase in the number of young women diagnosed with CCAC since 1970 that has been described in the American literature[1] appears also to have taken place in the Netherlands. However, one cannot be certain of this in the U.S., because the American registry has remained on a voluntary basis. Even when the registry was population-based, as in the state of Connecticut, it appeared that half of the CCAC cases had not been diagnosed as such.[13] A fortiori, underdiagnosis can be suspected in cases diagnosed before 1971. Also in the Netherlands, previous and possibly even recent underdiagnosis remains possible because PALGA includes only all patients diagnosed since 1988 and because it cannot be excluded that some CCACs are hidden under the diagnosis of "adenocarcinoma" or "carcinoma." Given the notoriety of a DES-CCAC relationship, it is quite possible that cases without reported exposure to DES have failed to be diagnosed as CCAC, but this could be ascertained only by a dedicated study of all vaginal and cervical tumors. From the current registry data, it appears that in 1988 the highest number of patients with CCAC were diagnosed and that the incidence appeared to decrease thereafter. The highest incidence in the U. S. was observed in 1975.[5] The recent higher incidence in the Netherlands corresponds with a later birth peak of the DES-exposed Dutch patients.[10] It also is possible that the different setup of the registry in the U.S., based on a voluntary entry, and the possibility of previous underdiagnosis, have contributed to the differences between the data in the U.S. and the Netherlands.

In the current Dutch registry, 47 of the 73 women with data on maternal history (64%) had, according to the authors' information, been exposed to DES. This percentage is comparable to that of the previous Dutch report on data until 1988 (63%), the registry of the U. S. in 1989 (60%), and two French series.[5,10,14,15] In the current study, 99% of women whose physician had information concerning the time of DES exposure had been exposed to DES before the 18th week of pregnancy. The most frequent reasons for DES being prescribed to the patients' mothers were problems in previous pregnancies, such as abortion or threatened abortion and abnormal blood loss.

The results of the cytologic examination showed a diagnosis of "malignant" or "suspected malignant" disease in 81% of the patients with cervical carcinoma and in 41% of patients with vaginal carcinoma. These results are similar to previous findings of the CNR in 1988.[10] Only cervical smears and no vaginal smears had been taken in those cases of CCAC of the vagina that had a cytologic diagnosis of "no abnormalities" or "atypia." This supports earlier observations that cytologic examination can make an important contribution to the diagnosis of CCAC if the smear-taking procedure is performed well, i.e., is comprised of separate smears from the cervix and from the four quadrants of the vagina.

Comparing the current findings with previous registry analysis, it appears that patients are increasingly being diagnosed at an earlier stage and after a shorter time interval between report of symptoms and diagnosis.[9,10] The patients who have been diagnosed since

1988 more often had a Stage I tumor (59%) than the patients who were entered in the registry before 1988 (31%). Since 1988, more patients (82%) had reported no symptoms at diagnosis, or reported symptoms of < 6 months' duration, than before 1988 (53%). This suggests that secondary prevention measures were successful.

Important parameters for the determination of prognosis of CCAC patients are stage, tumor size, growth pattern, nuclear atypia, and mitotic activity.[5,10,16,17] In the current study, an unfavorable prognosis corresponded with high stage, large tumor size, high grade of nuclear atypia, and high mitotic activity. The tubulocystic growth pattern corresponded with a better prognosis than the solid or mixed growth pattern. A classification criterion for the prediction of prognosis from the CNR in 1988 that was based on stage and nuclear atypia appeared in a follow-up study to correctly classify 95% of the patients.

It has been mentioned in the American literature that CCAC of the vagina and cervix may occur at an older age, but this has attracted little attention since then.[18] In a study by Kaminski and Maier from 1983, data were reported from 23 women with CCAC of the cervix who had not been exposed to DES, and who varied in age from 13 to 80 years.[19]. In the current study the authors examined the occurrence of CCAC of the vagina or cervix diagnosed between 1988 and 1993 in the whole population, regardless of the women's age and history of DES exposure. The age distribution of the 64 patients with CCAC who were diagnosed since 1988 showed 2 clearly separated peaks. The first contained 30 young women with a mean age of 26 years. The second contained 34 older women born before 1947, who had thus not been exposed to DES, with a mean age of 71 years. The first peak contained all DES daughters. If the DES daughters were excluded, the age distribution still showed a bimodal pattern, with a first peak at age 25–30 years. Such bimodal age distributions have been described for those types of cancer in which an important genetic factor has been determined (e.g., retinoblastoma, medullary carcinoma of the thyroid, and carcinoma of the colon).[20] Hereditary cases of carcinoma of the breast and ovary are strongly concentrated in the younger age group.[21]

The authors' finding of a clearly bimodal age distribution in women with CCAC has not been described previously. In the hypothesis that a population at risk exists, the bimodal age distribution is characteristic for the existence of a subpopulation with a strongly increased risk. DES exposure, which is thus far, to the authors' knowledge, the only researched risk factor, appears to be a risk factor, but does not provide an explanation for the prominent peak at a young age in women not exposed to DES. The maximum risks for non-DES-related CCAC thus occur at the ages of approximately 25 and 70 years, respectively. At least two explanations are possible: a risk period or a risk population.

Risk period

An interval of 10 to 20 years after menarche and menopause is in agreement with the estimated evolution time between the malignant transformation of the first cell and the diagnosis of several types of cancer such as carcinoma of the cervix.[22] The carcinogenic risk would thus strongly increase after the significant changes in the hormonal climate with the rise of the pituitary gonadotropin hormones, luteinizing hormone and follicle-stimulating hormone, that mark the menarche and menopause. The effects of this "hormone storm" could play a causal role. This hypothesis does not impact on the distribution of the risk within the population, and it is compatible with a low and homogeneous distributed risk, as well as with the existence of a subpopulation with a genetically or otherwise defined higher sensitivity for changes in the gonadotropin climate. Thus, in utero DES exposure would in both cases only increase an already existing risk of carcinogenesis. It is of clinical importance that this hypothesis would predict an increased incidence of CCAC in postmenopausal DES exposed women. Continued surveillance of these women after the age of 40 years would be warranted.

Risk population

Changes in the gonadotropin climate do not play a role in this hypothesis. The age peaks reflect two populations with a significantly different risk of CCAC. The highest number of women with a normal and low risk have a peak at older age, as is the case with most tumors whose incidence rate increases with age due to cumulative risks. The peak at a younger age must then be explained by a subpopulation with increased risk. This risk is either constitutional (genetic or otherwise), is based on exposure to exogenous agents other than DES, or a combination of the two (e.g., a constitutional sensitivity for carcinogens). In this hypothesis, DES could also increase an existing risk to develop CCAC at a young age. However, no increased incidence of CCAC is then expected in postmenopausal DES-exposed women.

Thus in both the risk period and the risk population hypotheses, factors other than DES also appear to play a role in the acceleration of carcinogenesis in the group of younger patients. These may be other exogenous or genetic risk factors.

Recently a familial chromosome translocation has

been described in chromosomes 3 and 6 {46,XX,t(3;6)(q29;q23)} in both a mother and her DES-exposed daughter.[23] The combination of the use of DES by the mother and the presence of a familial chromosome translocation in both herself and her daughter may, according to Leschot, occur frequently.[23] Elaborating on this, it may be possible that some of the chromosomal changes that occur in some women with multiple miscarriages may be linked to a potential for neoplastic transformation. A relationship between repeated spontaneous abortion, breast carcinoma, and an estrogen receptor gene variant has been described.[24,25] If a hypothesis concerning genetic factors for the occurrence of CCAC is supported, then the initiating neoplastic potential of DES should be reconsidered. Further research in this respect is necessary. Concentrating on DES as the only risk factor for CCAC may stand in the way of gaining increased knowledge of hormonal carcinogenesis.

Although DES has not been prescribed to women during pregnancy in the Netherlands for almost 20 years, the problems related to intrauterine DES exposure are still relevant. It is important to remain alert and to periodically update and evaluate the data of this registry, and to keep an open mind regarding the existence of additional or alternative risk factors.[26]

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