

Adverse Health Outcomes in Women Exposed In-Utero to Diethylstilbestrol

National Cancer Advisory Board

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ADENOCARCINOMA OF THE VAGINA IN ADOLESCENCE

A Report of 7 Cases Including 6 Clear-Cell Carcinomas (So-Called Mesonephromas)

ARTHUR L. HERBST, MD,* AND ROBERT E. SCULLY, MD†

Seven cases of adenocarcinoma of the vagina occurring in young women 15 to 22 years of age are reported. Six sought medical advice because of abnormal bleeding, which was assumed to be due to anovulation. Hormonal therapy delayed the correct diagnosis, which was not made until vaginal examination was performed. Vaginal smears contained rare suspicious or malignant cells in 3 cases but were negative in 3 others, indicating that cytologic examination is unreliable as a diagnostic aid. Six of the tumors were clear-cell carcinomas, or so-called mesonephromas, and one was an endometrioid carcinoma. The frequent presence of vaginal adenosis and other evidence suggested that the clear-cell carcinomas were of müllerian and not mesonephric origin. Although the follow-up has not been long, radical surgery with vaginal replacement and ovarian conservation appears to have been a safe and effective method of therapy.

ADENOCARCINOMA OF THE VAGINA*

Association of Maternal Stilbestrol Therapy with Tumor Appearance in Young Women

ARTHUR L. HERBST, M.D., HOWARD ULFELDER, M.D., AND DAVID C. POSKANZER, M.D.

Abstract Adenocarcinoma of the vagina in young women had been recorded rarely before the report of several cases treated at the Vincent Memorial Hospital between 1966 and 1969. The unusual occurrence of this tumor in eight patients born in New England hospitals between 1946 and 1951 led us to conduct a retrospective investigation in search of factors that might be associated with tumor appearance. Four matched controls were established for each patient; data were obtained by personal interview. Results show maternal

bleeding during the current pregnancy and previous pregnancy loss were more common in the study group. Most significantly, seven of the eight mothers of patients with carcinoma had been treated with diethylstilbestrol started during the first trimester. None in the control group were so treated (p less than 0.00001). Maternal ingestion of stilbestrol during early pregnancy appears to have enhanced the risk of vaginal adenocarcinoma developing years later in the offspring exposed.

Adenocarcinoma of the Vagina in Women Aged 14 to 22 at the MGH, 1966-1969

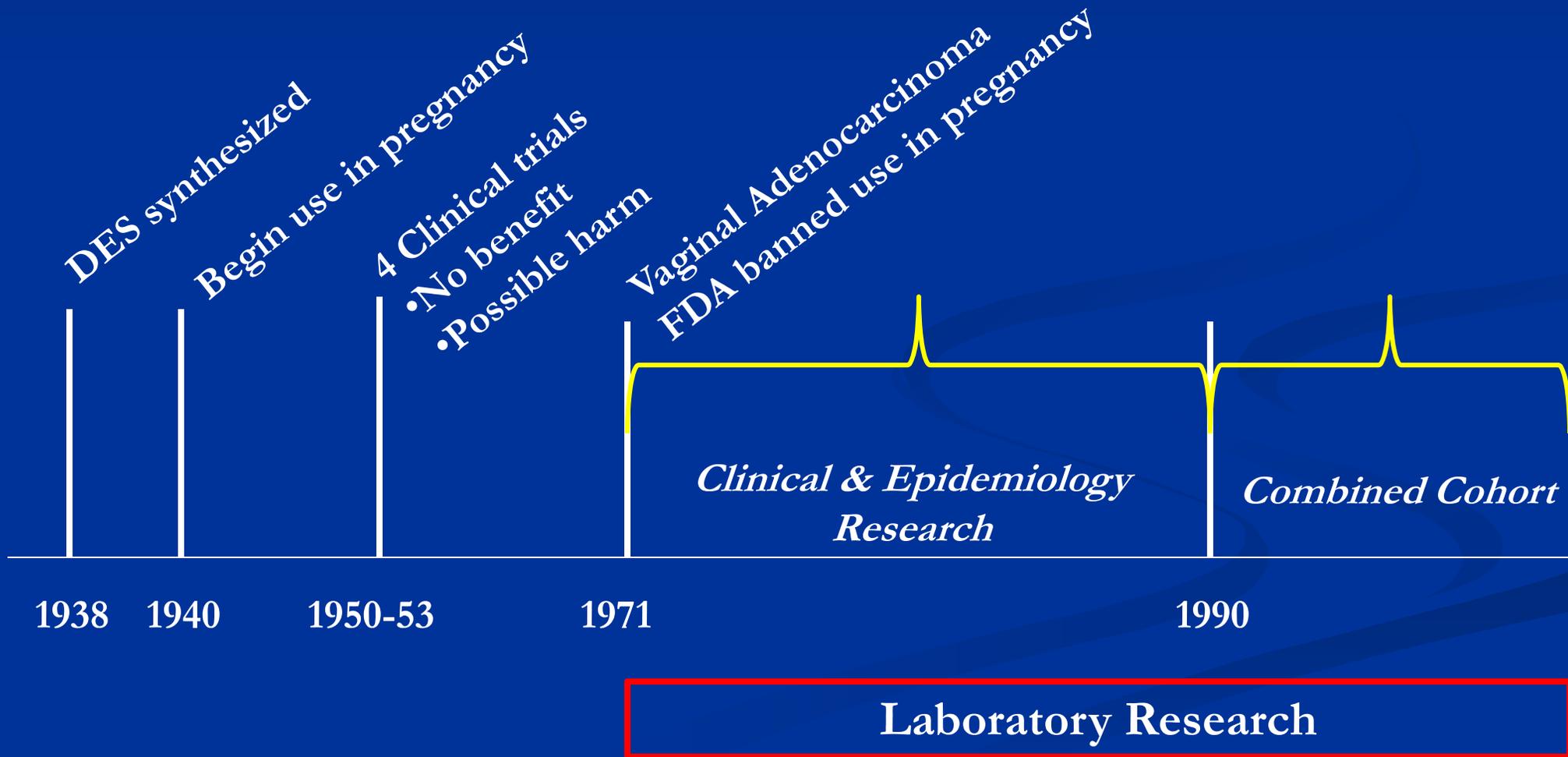
	Case	Control
In-Utero Exposure to DES		
+	7	0
-	1	32

$P < 1 \times 10^{-5}$

Far-ranging Impact

- First identified transplacental carcinogen
- Laboratory model for late effects of hormones and other agents
 - Gestation
 - Early-life
- Endocrine disruptors
- Epigenetic changes
 - Programming genes
 - Controlling cell differentiation
- Transgenerational carcinogenesis

Timeline



Typical DES Advertisement

- Ad appeared in a major medical journal in 1957
- “...to prevent ABORTION, MISCARRIAGE and PREMATURE LABOR”
- “Recommended for routine prophylaxis in ALL pregnancies...
96 per cent live delivery with *desPLEX* in one series of 1200 patients - bigger and stronger babies, too.”

“Really?”

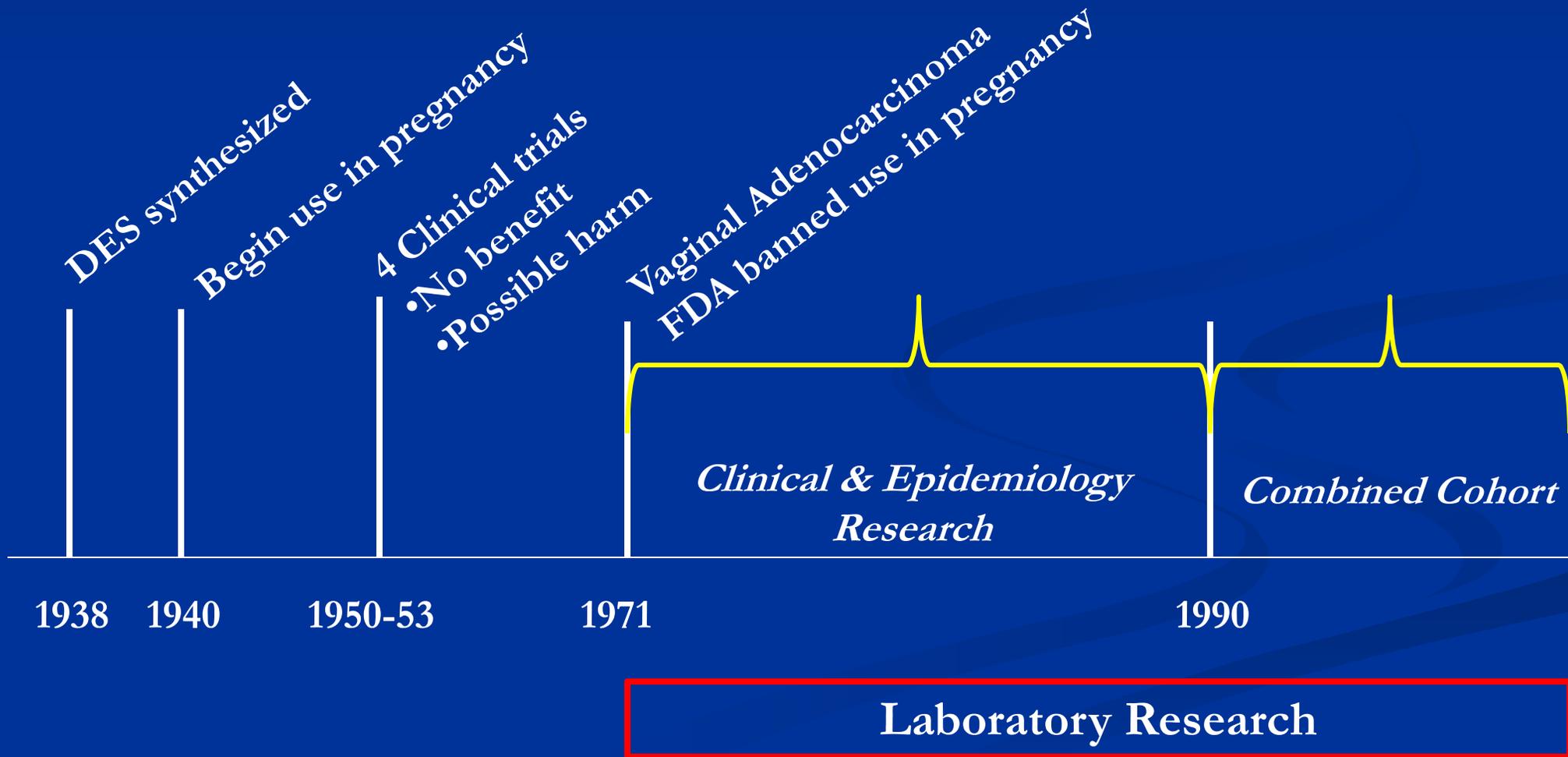
Yes...
desPLEX
to prevent ABORTION, MISCARRIAGE and
PREMATURE LABOR

*recommended for routine prophylaxis
in ALL pregnancies . . .*

*96 per cent live delivery with desPLEX
in one series of 1200 patients—
— bigger and stronger babies, too. . .*

*No gastric or other side effects with desPLEX
in either high or low dosage . . .*

Timeline



Other Outcomes of Concern

- Other cancers
 - Breast
 - Other gynecologic
- Many other adverse outcomes suggested

Combined Cohort Study of Gestational DES Exposure

	Eligible Participants	
	Exposed	Unexposed
Mothers		
4 cohorts, 7 centers	5441	4036
Sons		
4 cohorts, 5 centers	2001	2111
Daughters		
4 cohorts, 9 centers	5067	2387
DESAD	4009	1032
Dieckmann	414	393
Women's Health Study	331	719
Horne	313	243
Granddaughters		

ORIGINAL ARTICLE

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Linda Titus-Ernstoff, Ph.D., and Rebecca Troisi, Sc.D.

Hoover RN et al. N Engl J Med 2011;365:1304-1314

Twelve Adverse Health Outcomes Associated with In-Utero Exposure to DES in the Combined Cohort Study of DES Exposure

- Clear-cell Vaginal Cancer
- Cervical Dysplasia (CIN2+)
- Breast Cancer
- Spontaneous Abortion
- Ectopic Pregnancy
- Second Trimester Pregnancy Loss
- Infertility
- Preeclampsia
- Pre-term Birth
- Premature Menopause
- Stillbirth
- Neonatal Death

Hazard Ratios for Adverse Health Outcomes in Women with and without DES Exposure

Adverse Outcome	Hazard Ratio (95% CI)
Clear-cell adenocarcinoma	39 (15 to 104)
Breast cancer at ≥ 40 yr	1.82 (1.04 to 3.18)
Cervical intraepithelial neoplasia, grade ≥ 2	2.28 (1.59 to 3.27)
Infertility	2.37 (2.05 to 2.75)
Spontaneous abortion	1.64 (1.42 to 1.88)
Ectopic pregnancy	3.72 (2.58 to 5.38)
Loss of second-trimester pregnancy	3.77 (2.56 to 5.54)
Preterm delivery	4.68 (3.74 to 5.86)
Preeclampsia	1.42 (1.07 to 1.89)
Stillbirth	2.45 (1.33 to 4.54)
Neonatal death	8.12 (3.53 to 18.65)
Early menopause	2.35 (1.67 to 3.31)

Cumulative Risks of Adverse Health Outcomes in Women with and without DES Exposure and the Excess Risk Due to Exposure

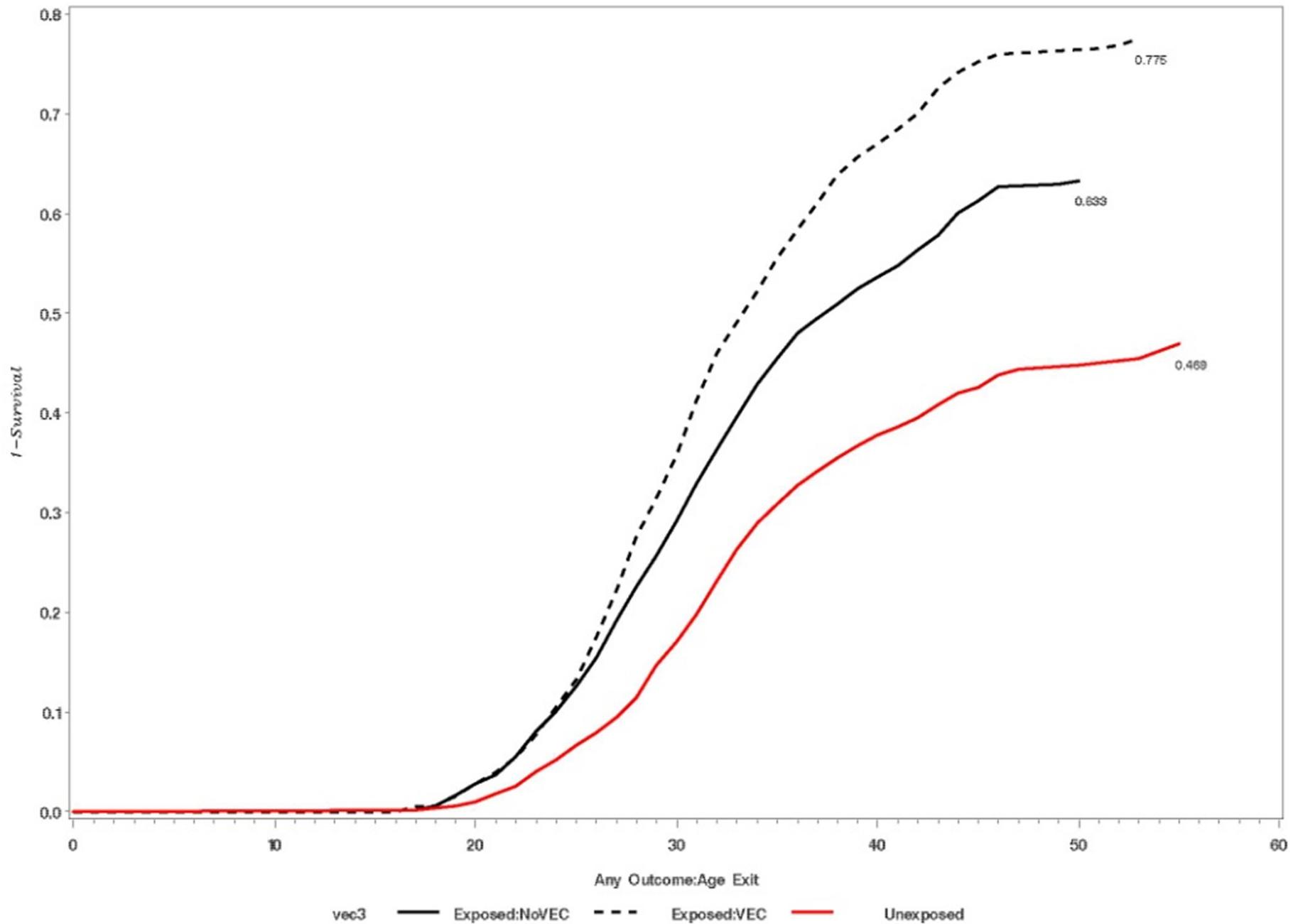
Adverse Outcome	Cumulative Risk Exposed <i>percent</i>	Cumulative Risk Unexposed <i>percent</i>	Excess Risk (95% CI)
Clear-cell adenocarcinoma	0.1	0.0	0.1 (0.0 to 0.3)
Breast Cancer at ≥ 40 yr	3.9	2.2	1.7 (-1.4 to 4.7)
Cervical intraepithelial neoplasia, grade ≥ 2	6.9	3.4	3.5 (1.5 to 5.4)
Infertility	33.3	15.5	17.8 (14.5 to 20.9)
Spontaneous abortion	50.3	38.6	11.7 (3.3 to 20.1)
Ectopic pregnancy	14.6	2.9	11.7 (8.9 to 14.5)
Loss of second-trimester pregnancy	16.4	1.7	14.7 (8.5 to 20.9)
Preterm delivery	53.3	17.8	35.4 (27.3 to 43.6)
Preeclampsia	26.4	13.7	12.7 (4.5 to 20.9)
Stillbirth	8.9	2.6	6.3 (-0.8 to 13.3)
Neonatal death	7.8	0.6	7.2 (1.9 to 12.5)
Early menopause	5.1	1.7	3.4 (2.1 to 4.7)

Vaginal Adenosis: Effective Biologic Dose Marker?

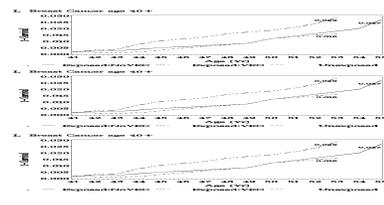
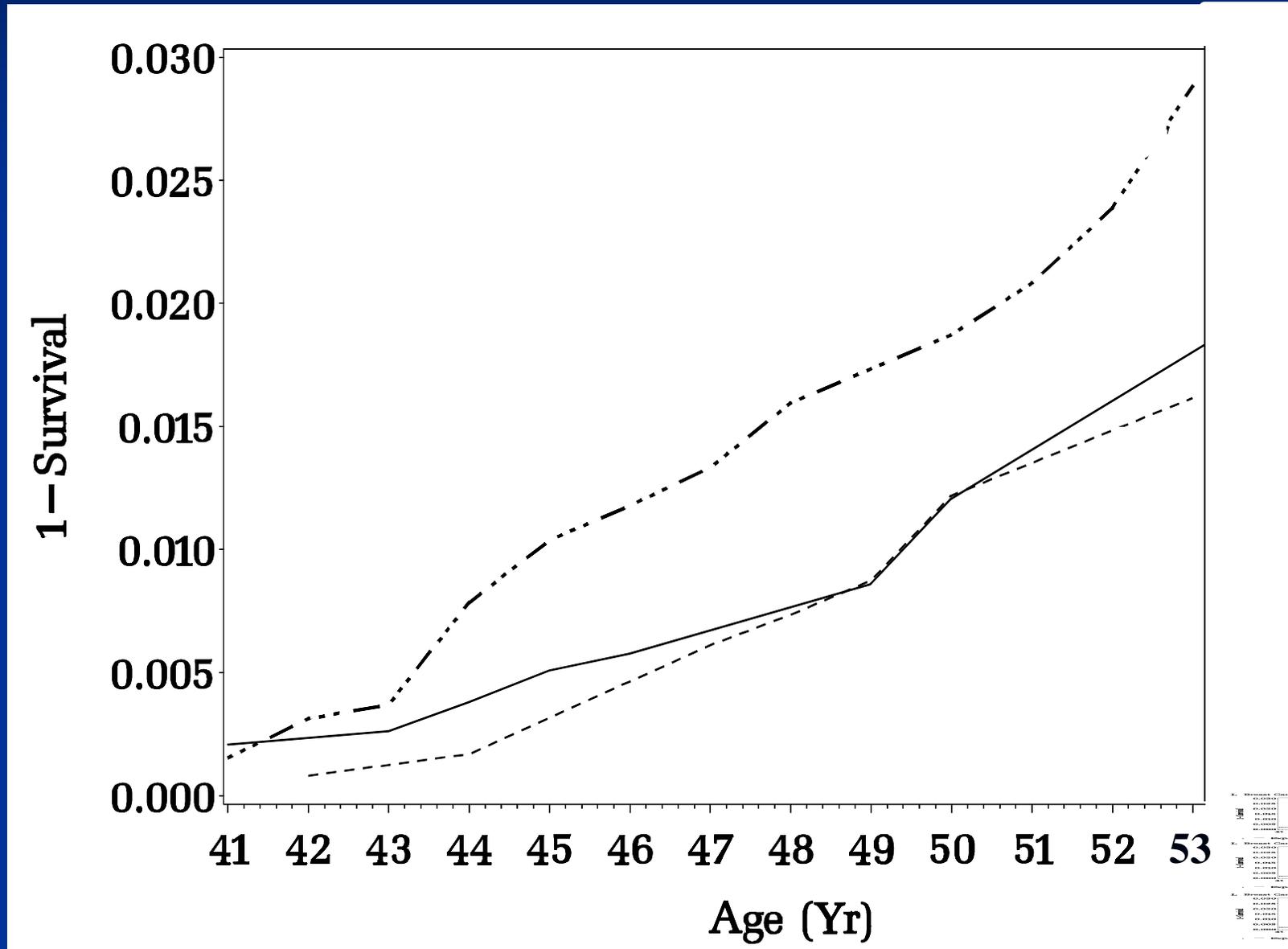
- Persistent Mullerian columnar epithelium in the anterior wall and upper 1/3 of vagina
- Manifestation of maternal DES exposure
- Red, granular patches
- Precursor of clear cell adenocarcinoma



Cumulative Risk: Any Outcome by VEC



Cumulative Risk of Breast Cancer \geq age 40 by DES Exposure and Vaginal Adenosis



Conclusions

The NEW ENGLAND JOURNAL of MEDICINE

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CONCLUSIONS

In utero exposure of women to DES is associated with a high lifetime risk of a broad spectrum of adverse health outcomes. (Funded by the National Cancer Institute.)

N ENGL J MED 365;14 NEJM.ORG OCTOBER 6, 2011

CONCLUSIONS

A DES Daughter
“For us, it was a train wreck”

Lessons to be (Re)Learned

- We need clinical trials.
- Early life and gestation are vulnerable time periods.
- “Alert clinicians” and “alert mothers” notice the unusual.
- We need systematic, long-term post-marketing surveillance.

NCI DES Combined Cohort Study Steering Committee



Hazard Ratios for In Utero Exposure to DES and Any Adverse Outcome by Date

	HR	95% CI
Total	2.08	1.89-2.28
< 1976	2.17	1.75-2.69

Number of Cases, Hazard Ratios, and Confidence Intervals for In-Utero Exposure to DES

ANY RISK				
	# of Cases		HR	95% C.I.
	Unexposed	Exposed		
Overall	707	2339	2.08	1.89-2.28
DESAD	328	1976	1.99	1.77-2.24
Dieckmann	125	206	2.17	1.73-2.72
WHS	254	187	2.12	1.75-2.56

Controlled Clinical Trials of DES in Pregnancy

Study	# of subjects		Results
	+ DES	- DES	
Swyer et al., (1953)	233	227	No effect: Preeclampsia, prematurity
Dieckmann et al., (1953) *	840	806	No effect: Spontaneous abortion, preeclampsia, stillbirth, neonatal death, prematurity, birthweight
British MRC, (1955) (Diabetics)	76	71	No effect: fetal loss, stillbirth, neonatal death
Ferguson (1953)	190	203	No effect: Preeclampsia, prematurity, spontaneous abortion, fetal weight or survival

*Increased Risk: Spontaneous abortion (p=0.04), Neonatal death (p=0.01), Prematurity (p=0.03)

Cumulative Risks of Adverse Health Outcomes in the DESAD and Dieckmann Cohorts, According to DES Exposure Status, and in the DES-Exposure Group, the Presence or Absence of Vaginal Epithelial Changes (VEC) at Entry Examination

