FACTSHEET
Diethylstilbestrol (DES) and Cancer

KEY MESSAGES

- Although the majority of persons exposed to DES will not experience any negative health effects, available research findings indicate that exposure to DES increases the risk of the following health problems:
    - Women who took DES during pregnancy have a small increased risk for breast cancer.
    - Women exposed to DES in utero (**DES daughters**) are at increased risk for clear cell adenocarcinoma of the vagina/cervix, structural abnormalities in the reproductive tract, miscarriage, tubal (ectopic) pregnancy, infertility and premature birth. Women over 40 years of age who were exposed to DES in utero are at increased risk of breast cancer.
    - Men exposed to DES in utero (**DES sons**) are at increased risk of abnormally small testes, undescended testes and non-cancerous epididymal cysts.
    - Research into the health of DES grandsons and granddaughters has not found conclusive evidence of an increased cancer risk except for the possibility of a heightened ovarian cancer risk in DES granddaughters. Research studies on this group are continuing.

- Relevant health care providers such as General Practitioners, midwives and women's health nurses who are familiar with DES can assist individuals affected by DES to identify possible complications.

- Women prescribed DES while pregnant and DES daughters who are over the age of 40 are advised to follow normal screening recommendations for their age groups. They should also be *'Breast Aware'* by familiarising themselves with the normal look and feel of their breasts, and report any unusual breast changes to their doctor, irrespective of both the time since their most recent mammogram and the results of that mammogram.

- Routine Pap testing is not an adequate gynaecological cancer screening test for DES daughters. An annual DES-specific pelvic examination is required (see page 4).

- DES daughters planning pregnancy should alert their clinician of exposure prior to conception so they can be evaluated for cervical and uterine abnormalities. During pregnancy, DES daughters should be treated as 'high risk' patients.

- DES sons should regularly check for lumps or swellings on the surface of the testes and promptly report any testicular masses, blood in the urine, or genital complaints to their doctor.

- Continued monitoring of the third generation of individuals whose grandmothers were exposed during pregnancy to DES is needed to conclusively determine whether there is an increased risk of cancer in this population.

Diethylstilbestrol

Diethylstilbestrol (DES), a synthetic form of the female hormone oestrogen first manufactured in 1938, was prescribed in Australia in the late 1940s and 1950s, less often in the 1960s and 1970s, and was prescribed in some instances beyond 1971.[1] DES was primarily given to prevent miscarriage and other pregnancy complications, such as tubal pregnancy and early delivery.[2] Other therapeutic uses included suppression of lactation and post menopausal syndrome.[3] Separately it was later used as a growth promoter in chicken, sheep and cattle.[4]

More than 30 years of research have confirmed that DES is a teratogen, an agent that can cause malformations in an embryo or foetus.[2] Research demonstrates that exposure to synthetic oestrogens during critical stages of foetal development (that is, in utero) increases the risk of abnormalities which can result in structural, functional, or long-term pathological changes including cancer.[2,5]

DES was never patented. Many companies manufactured and marketed it under more than 200 different brand names.[6,7] It was most commonly administered in tablet form, but was also given as injections, vaginal suppositories and sometimes as an ingredient in pregnancy vitamins.[8]

Over 10 million people were exposed to DES worldwide.[8] Many people remain unaware of their exposure and the potential adverse health effects of DES.[1]

Adverse health effects of DES

Individuals exposed to DES are at increased risk of certain health problems compared to the general population. Those placed at risk include women who were prescribed the treatment during pregnancy, children in the womb at the time their mother was taking the treatment (sons and daughters) and possibly the next generation (the children of DES sons and daughters). However it is important to note that the majority of individuals exposed to DES will not experience negative health consequences.

Women who took DES while pregnant

Research indicates a small increased risk for breast cancer among those women who took DES while pregnant (relative risk of approximately 1.3 or an absolute risk of 13.3% versus 10.2% among unexposed women).[9,10,11] While in Australia the odds of developing breast cancer in the general female population are one in eleven, this figure increases to one in six for DES exposed women.[12]

Children exposed to DES in utero

Children born between 1938 and 1971 to mothers who were taking DES while pregnant are also at risk of health problems. The complete range of risks to individuals exposed to DES in utero is uncertain at this time, but current research evidence indicates that women are at an increased risk of breast cancer and cancer of the vagina and cervix.

Breast cancer

A prospective study published in 2006 found that women exposed to DES in utero have a 1.9 fold increased risk of breast cancer after the age of 40 years.[13] Among these DES

daughters, the risk is similar to having a first degree relative such as a mother or sister with breast cancer, placing them in a higher risk group.

Vaginal and cervical cancer
In the early 1970s, it was demonstrated that women exposed to DES in utero developed a rare form of cancer of the vagina and cervix called clear cell adenocarcinoma (CCA) at a rate around 40 times higher than the non-exposed population.[14,15] In absolute terms, around 1.5 cases will be found per 1000 women exposed to DES in utero.[16] This cancer tends to appear in DES daughters as they reach their late teens and early 20s.[14] Women diagnosed with CCA of the vagina and cervix before the age of 40 years are highly likely to be DES daughters.[17] This cancer has been detected among DES daughters in their 40s and 50s.[18]

Non-cancer risk
Apart from the small risk of cancer, DES daughters may have structural abnormalities in the vagina, uterus or cervix. Benign vaginal growths are seen in approximately 33% of exposed women.[19,20] Cervical malformations are found in 25-33% of the exposed population.[21] Uterine malformations are likely in up to 69% of DES daughters.[22] DES daughters are also at an increased risk of irregular menstruation, miscarriage, tubal (ectopic) pregnancy, infertility and premature birth.[23,24]

Current research evidence indicates that DES sons (sons of women who took DES while pregnant with them) are at risk of abnormally small testes, undescended testes (where the testes do not drop into the scrotum) and non-cancerous epididymal cysts (growths on the testes).[25,26] Although there is no established link between DES exposure and cancer in human males, such a link has been demonstrated in animal studies.[27,28,29,30,31] However, testicular cancer is more common in men with uncorrected undescended testes.[32]

Third generation
The next generation of children (the children of individuals exposed to DES in utero) may also be at risk of health problems. These grandchildren of women prescribed DES during pregnancy are frequently referred to as the 'third generation'. Although very few studies to date have focused on health problems in third-generation humans, animal studies looking at DES exposed offspring have generated concerns about uterine and rare tumour of the testis.[33,34] A study published in 2008 assessed cancer and benign pathology diagnoses occurring in the children of women exposed to DES in utero.[35] The findings of the study did not support an overall increase of cancer risk in the sons or daughters of women prenatally exposed to DES, but the number of ovarian cancer cases was greater than expected.[35] The results of this study emphasise a need to continue to monitor the 'third generation' population to determine whether this group is at increased risk of cancer.[35]

Awareness
A woman who had problems with a pregnancy between late 1938 and 1971 may have been given DES. Treating doctors or hospitals may still have medical records that could clarify this. Health care providers such as General Practitioners, midwives and women's health nurses can help to identify and support individuals exposed to DES.

Screening and surveillance

Appropriate cancer screening of the population of women exposed to DES will contribute to earlier stage diagnosis and provide a greater chance for survival.

Women prescribed DES while pregnant and DES daughters over the age of 40 are advised to follow normal screening recommendation for their age groups. A mammogram is not a reliable screening test for women younger than 40 years as the density of breast tissue before this age often makes it difficult to detect cancers. Women of any age who are at increased risk of breast cancer are encouraged to discuss relevant screening options including breast ultrasound with their doctor. Women should also be *'Breast Aware* ' by familiarising themselves with the normal look and feel of their breasts and consult a doctor promptly regarding unusual breast changes, irrespective of both the time since their most recent mammogram and the results of that mammogram. Given that many breast cancers cannot be felt, the *Breast Awareness* approach should be seen as a supplement to, not a substitute for, regular mammograms.

Although it is very rare, DES daughters should be warned about their increased risk of CCA of the vagina and cervix and should be carefully monitored for CCA throughout their lives. It is important for these women to understand that their special circumstances dictate that a routine Pap test is not an adequate cancer screening test for them and that a special DES recommended annual pelvic examination, also known as the 'DES exam', is required and should be offered annually. The DES examination involves:

- A careful visual inspection and feeling with the fingers or hand of the entire vagina;
- Separate Pap smears from the cervix and from the surfaces of the upper vagina; and
- An internal pelvic examination.

Depending on the results of these tests, further procedures may be necessary, such as colposcopy and biopsy. It is important that persons exposed to DES obtain the recommended follow-up.

DES daughters planning pregnancy should alert their clinician of exposure prior to conception so that they can be evaluated for cervical and uterine abnormalities. DES daughters are at an increased risk of pregnancy complications. During pregnancy they should be treated as high-risk patients.

DES sons should regularly check for lumps or swellings on the surface of the testes and promptly report any testicular masses, blood in the urine, or genital complaints to their doctor.

Hormone Replacement Therapy and DES

Both Hormone Replacement Therapy (HRT) and using DES while pregnant have been independently associated with an increased risk of breast cancer. Available research suggests that there is no interactive effect between DES exposure and HRT. In other words, HRT does not appear to increase the risk of breast cancer beyond the risk associated with either DES exposure or HRT alone.[36] Decisions on commencement or continuation of HRT should be fully informed, based on each woman's individual circumstances, and made in consultation with a health care provider.

Research
Researchers continue to follow the health of individuals exposed to DES to determine whether other health problems occur as they grow older. Since 1992, the United States National Cancer Institute, in collaboration with research centres throughout the United States has conducted a longitudinal cohort study, known as the DES Follow-Up Study, of more than 21,000 mothers, daughters, and sons. This follow-up study investigates the long-term health risks associated with exposure to DES. More information on the study can be found at http://www.desfollowupstudy.org/

The following websites are recommended for further information and support:
US Centre for Disease Control. http://www.cdc.gov/des/index.html

National Cancer Institute. http://www.cancer.gov/cancertopics/factsheet/Risk/DES

The following website lists the names under which DES has been sold in Australia
http://desnsw.blogspot.com.au/2009/05/des-brands-galore.html

Advice, support and information are also available through:
DES Action Australia - NSW
Ph: (02) 9875 4820
www.desnsw.blogspot.com.au

DES Action Australia
PO Box 282, Camberwell VIC 3124
desact@vicnet.net.au
www.desaction.org.au

DES Action USA
PO Box 7296, Jupiter, FL 33468, USA
www.desaction.org
info@desaction.org
Ph: 1800 337 9288

Cancer Council Helpline on (freecall) 13 11 20

DES Daughters Listserv and Online Support Group (An online support group to promote discussion, support, and sharing of information among DES Daughters)
http://www.desaction.org/onlinesupportgroup.htm

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