EXOGENOUS OESTROGENS AND THE RISK OF BREAST CANCER*

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Many epidemiological studies of the aetiology of breast cancer point to an association between endogenous oestrogens and breast cancer. Exogenous oestrogen administration may also carry a risk of the disease. The published data will be presented and discussed.

GENERAL EPIDEMIOLOGICAL EVIDENCE

Epidemiological studies of risk factors for breast cancer have revealed many associations which have been extensively reviewed.[1-3] Associations with menstrual and reproductive factors are of special relevance in the present context. Most studies have found that an early menarche is associated with an increase in risk (up to threefold, if extreme groups are contrasted), while an early natural menopause (and artificial menopause produced by bilateral oophorectomy) protects against the disease (again, up to a threefold difference in risk, if extreme groups are contrasted). Early age at first full-term pregnancy has an important protective effect in the great majority of studies, while there is some additional protective effect of high parity. No clear consensus exists about the influence of incomplete pregnancies (some studies suggesting a harmful effect and others no effect) while likewise there is continuing debate about the effect, if any, of lactation (some studies suggesting a protective effect and others no effect). An interesting recent finding is that mothers of twins appear to have only about 70% of the breast cancer risk experienced by other women.[4]

The effects of age at menarche and age at menopause point clearly to the importance of ovarian function in the aetiology of breast cancer and, rather less directly, to the likely importance of oestrogens. The interpretation of the reproductive risk factors in endocrinological terms is, however, more uncertain. Notwithstanding, a number of authors have put forward hypotheses in an attempt to draw the epidemiological observations together into an unifying hypothesis. These hypotheses are not reviewed here; nonetheless, it should be noted that a great deal of effort has been devoted to studies examining the relationship between breast cancer, and blood or urine oestrogen levels. Twenty of these (together with some new data) have been summarised recently by Key *et al*[5] with the conclusion that high levels of endogenous oestrogens in postmenopausal women are associated with increased breast cancer risk. The same conclusion was reached very recently by Hankinson *et al*[6] using data from the Nurses' Health Study in the USA. The relationship between endogenous oestrogens and breast cancer risk in premenopausal women is, however, more uncertain.

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EXOGENOUS OESTROGEN ADMINISTRATION

If oestrogens are important in the aetiology of breast cancer, effects on risk might be expected from their administration for therapeutic reasons. Oestrogens (either alone or with progestogens) have been given to women on a large scale in three particular circumstances: (a) during pregnancy, to try to prevent abortion and late pregnancy toxaemia; (b) during the childbearing years to prevent pregnancy; and (c) around the time of the menopause and subsequently to relieve menopausal symptoms and to try to prevent the development of osteoporosis.

Administration of oestrogens during pregnancy

Stilboestrol, a synthetic non-steroidal oestrogen, was promoted in the 1940s and 1950s for the treatment of habitual abortion, threatened abortion and late pregnancy toxaemia.[7] The dosages recommended were large, up to 15 g of the drug between the seventh and thirty-fifth week of pregnancy. It may be noted that the effect of this treatment on pregnancy outcome was later shown not merely to be ineffective, but to be actually harmful.[8]

In 1971, it was discovered that girls born to mothers who had taken stilboestrol in pregnancy were at an increased risk of clear cell adenocarcinoma of the vagina and cervix.[9] Later, other effects became apparent (in exposed daughters and exposed sons), but to date, there is no evidence of an increased breast cancer risk in exposed daughters.[10] There is, however, concern about the occurrence of this disease in the mothers themselves. A number of studies have examined this question, but the most important are those reported by Colton *et al* in 1993,[11] and by Calle *et al* in 1996.[12] The first of these studies included 3,029 stilboestrol-exposed mothers and a similar number of unexposed mothers who had delivered live babies at four centres in the USA between 1940 and 1960.[11] The relative risk of breast cancer associated with stilboestrol exposure was 1.35 (95% confidence interval, 1.05-1.74). The difference between the groups did not begin to emerge until about 15 years after exposure. The study by Calle *et al*[12] involved the occurrence of fatal breast cancer in a cohort of 501,536 parous women in the USA who had no previous history of cancer when they were recruited in 1982. Stilboestrol exposure during pregnancy was reported by 3.9% of the women. After nine years of follow-up, 1,574 deaths from breast cancer had occurred in the cohort. The relative risk of fatal breast cancer associated with stilboestrol exposure was 1.34 (95% confidence interval, 1.06-1.69). The excess risk did not appear to increase with time since exposure, although this study provided relatively few data relating to intervals since exposure of less than 30 years.

On balance, the available data thus support the view that stilboestrol acts as a weak human carcinogen with respect

to the breast, when given during pregnancy.

Administration of oestrogens and progestogens to prevent pregnancy
The possible relationship between oral contraceptive use and the risk of breast cancer has stimulated an enormous amount of epidemiological research around the world over the last 30 years. There has been some variation in the results of the different studies and, until recently, no consensus about the interpretation of the available data.

In 1992, a Collaborative Group on Hormonal Factors in Breast Cancer was established to bring together, reanalyse and publish the worldwide data. This mammoth undertaking was coordinated by a Scientific Secretariat based within the Imperial Cancer Research Fund Cancer Epidemiology Unit at Oxford, England, and was led by Professor Valerie Beral. It was decided at the outset that the relevant data would be sought from the original investigators for each individual woman so that standard analyses could be conducted across the entire database.

The results in relation to hormonal contraceptive use were published in 1996.[13,14] Individual data about 53,297 women with breast cancer and 100,239 control women without breast cancer from 54 studies conducted in 25 countries were collected, checked and analysed centrally. These data represented about 90% of the worldwide epidemiological evidence on breast cancer risk and use of hormonal contraceptives. What was known about the 12 studies for which data were not included suggested that their results would have been consistent with the main findings.

With regard to combined oral contraceptives, the main findings were extremely simple. First, the relative risk of having breast cancer diagnosed in current users of combined oral contraceptives in comparison with never-users was 1.24 (95% CI, 1.15-1.33). There was also some increase in risk in ex-users, but this was no longer apparent ten or more years after stopping (Table 1). Secondly, women who began use of combined oral contraceptives before the age of 20 had higher relative risks of having breast cancer diagnosed while using the preparations (1.59, 95% CI, 1.40-1.78) and within five years after stopping (1.49, 95% CI, 1.30-1.68) than women who began use at older ages. However, amongst women commencing use of the combined pill before age 20, there was no significant increase in risk for longer intervals since stopping (5-9 years 1.07, 95% CI, 0.93-1.21, 10-14 years 1.13, 95%CI, 0.98-1.27, 15 or more years 1.14, 95% CI, 0.98-1.29). Finally, cancers diagnosed in women who had used combined oral contraceptives were clinically less advanced than those diagnosed in women who had never done so. Apart from the above, no other factor (such as duration of use, dose and type of oestrogen or dose and type of progestogen) had any important effect on risk. In addition, although numerous variables were assessed to see if there was statistically significant evidence that they modified the relative risk associated with combined oral contraceptive use, none but age at first use actually did so (see above).

TABLE 1
Relative risk of diagnosis of breast cancer in relation to recency of use of combined oral contraceptives. (Findings modified from the Collaborative Group on Hormonal Factors in Breast Cancer.)[13]

Recency of use of combined oral contraceptives	**Relative risk ± FSE**	**No. cases/ No. controls**
Never	1.00 ± 0.014	28,200/ 55,220
Current	1.24 ± 0.038	2,356/4,328
1-4 yrs since last use	1.16 ± 0.032	2,717/4,851
5-9 yrs since last use	1.07 ± 0.024	4,239/7,688
10-14 yrs since last use	0.98 ± 0.022	4,384/8,182
15 or more yrs since last use	1.03 ± 0.025	4,434/8,285

Relative risks stratified by study and adjusted for relevant confounding variables. FSE = Floating Standard Error.

Not surprisingly, the Collaborative Group gave careful consideration to absolute risks since it is risks of this type which are of most importance from the public health point of view. Results were generally reassuring; for example, among 10,000 women from Europe or North America who used combined oral contraceptives from age 16-19, from age 20-24 and from age 25-29, the estimated excess numbers of cancers diagnosed up to ten years after stopping use were 0.5 (95% CI, 0.3-0.7), 1.5 (95% CI, 0.7-2.3) and 4.7 (95% CI, 2.7-6.7) respectively. It was also stressed that the results obtained might be due to earlier diagnosis of breast cancer in pill users, biological effects of the pill, or a combination of reasons.

The Collaborative Group's analysis yielded little information about progestogen-only oral contraceptives (used by only 0.8% of the study population) or injectable progestogens (used by only 1.5%). Nonetheless, so far as they went, the results were broadly similar to those for combined oral contraceptives.

While the Collaborative Group's report must be regarded as definitive with regard to information available up to the mid-1990s, it is not, of course, the last word for all time. Further work will be required on newer contraceptive preparations and on changing patterns of use. In particular, the report notes that 'when the new data on the long-term effects of early use become available, it will be necessary to re-examine the worldwide evidence'.

Administration of oestrogens with or without progestogens around the time of the menopause and subsequently
As with oral contraceptives, large numbers of studies have been reported which are concerned with the possible relationship between use of hormone replacement therapy (HRT) and breast cancer risk. Apart from one very small randomised trial, all these studies are of the observational type. There are, however, two large-scale randomised controlled trials of the long-term effects of HRT which are either in progress (the Women's Health Initiative in the United States of America) or are in the process of starting (the Medical Research Council supported trial developed by Meade and colleagues in the United Kingdom). Unfortunately, even if these trials are successful in the long term (which is open to doubt), useful information about breast cancer is unlikely to emerge for at least ten years.

Accordingly, we are driven to make the best possible use of the observational studies.

Reference has already been made to the recent publication concerning oral contraceptives by the Collaborative Group on Hormonal Factors in Breast Cancer.[13] Even more recently, the Collaborative Group has published a similar overview concerning the use of HRT and breast cancer.[15] Individual data relating to 17,949 postmenopausal women with breast cancer and 35,919 postmenopausal control women without breast cancer, from 51 studies in 21 countries, were obtained, checked and analysed. As with the oral contraceptive analysis, the data covered about 90% of the relevant worldwide epidemiological evidence on breast cancer risk and HRT use.

It was found that age at menopause was a particularly important confounding variable to consider in the analysis. Thus women with an early menopause are particularly likely to start HRT at a young age and to use it for a long time, while the reverse is true for women with a late menopause. Since early menopause itself offers substantial protection against the risk of breast cancer, it is obvious that failure to allow for the effect of this variable in an analysis could lead to failure to detect an adverse effect of HRT.

As with the oral contraceptive analysis, three main measures of exposure were used in the HRT analysis - total duration of use, time since first use and time since last use. These three exposure variables are, of course, all correlated. After careful assessment, only total duration of use and time since last use were found to be of importance as shown in Table 2. Thus an increase in the risk of having breast cancer diagnosed was limited to current HRT users and those who had ceased HRT use less than five years previously. Amongst these women, it was estimated that the relative risk of having breast cancer diagnosed increased by a factor of 1.023 (95% CI, 1.011-1.036) for each year of HRT use. As was found in the oral contraceptive analysis, cancers diagnosed in women who had used HRT were clinically less advanced than those diagnosed in women who had never done so. This finding might reflect earlier diagnosis of breast cancer in HRT users, a biological effect of HRT or a combination of reasons.

TABLE 2

Relative risk of diagnosis of breast cancer in relation to recency of use and duration of use of HRT. (Findings modified from the Collaborative Group on Hormonal Factors in Breast Cancer.)[15]

Recency of use and duration of use of HRT	Relative risk ± FSE	No. cases/ No. controls
Never user	1.00 ± 0.021	12,467/ 23,568
<5 yrs since last use		
Duration <1 yr	0.99 ± 0.085	368/860
" 1-4 yrs	1.08 ± 0.060	891/2,037
" 5-9 yrs	1.31 ± 0.079	588/1,279
" 10-14 yrs	1.24 ± 0.108	304/633
" ≥15 yrs	1.56 ± 0.128	295/514
≥5 yrs since last use		
Duration <1 yr	1.12 ± 0.079	437/890
" 1-4 yrs	1.12 ± 0.068	566/1,256
" 5-9 yrs	0.90 ± 0.115	151/374
" ≥10 yrs	0.95 ± 0.145	93/233

Relative risks stratified by study and adjusted for relevant confounding variables. FSE = Floating Standard Error.

A careful search was undertaken to identify any variables which might modify the magnitude of the relative risks of having breast cancer diagnosed associated with HRT use. Of 42 comparisons made, only two closely-related factors had a statistically significant risk-modifying effect, namely body weight and body mass index. Thus the increased risks associated with HRT use were found to be largely confined to women weighing less than 65 kg ,and those with a body mass index less than 25 kg/m^2. These findings are potentially of considerable clinical importance.

The collaborative reanalysis of the data on HRT and breast cancer has a number of important limitations. First, the data are insufficient to enable adequate study of individual HRT constituents, and little information is available about combined products. Secondly, the cases were diagnosed on average in 1985, so there is inevitably a lack of information about modern HRT preparations. Thirdly, few women included in the analysis were over the age of 70 years. Finally, the study results are concerned with breast cancer diagnosis and not with breast cancer mortality - an important point given the more favourable staging of the cancers occurring in HRT users.

An interesting finding in the HRT analysis was the close similarity in the magnitude of the risk associated with HRT use on the one hand and with increasing age at menopause on the other. Thus, as already indicated, among current and recent HRT users the relative risk of having breast cancer diagnosed increased by a factor of 1.023 (95% CI, 1.011-1.036) for each year of HRT use. When the analysis was limited to women never using HRT, it was found that the relative risk of having breast cancer diagnosed rose by a factor of 1.028 (95% CI, 1.021-1.034) for each year of increase in age at menopause. These findings make it tempting to think of the administration of HRT as essentially delaying the menopause, although this is obviously a very simplistic idea.

As with the oral contraceptive report, the HRT report included information about the magnitude of absolute risks. As an example, consider a sample of 10,000 women from Europe or North America, aged 50 years, who do not take HRT at any time. By the age of 70 years, 630 will have been diagnosed as having breast cancer. Now consider an equivalent sample of women who start HRT at age 50 years, take it for 15 years, and then stop. By the age of 70 years, 750 will have been diagnosed with breast cancer, an excess of 120 cases per 10,000 over a 20 year period.

As indicated earlier, information about breast cancer risk in relation to HRT use will eventually emerge from the two large clinical trials currently in progress. Further observational information based on a vastly greater population will be available within a couple of years from the Million Women Study based on the National Health Service Breast Screening Programme. This project is being co-ordinated by Professor Valerie Beral and her colleagues in the ICRF Cancer Epidemiology Unit at Oxford.

One or two other issues are worth mentioning in relation to HRT use and breast cancer. First, there is

considerable interest in the question as to whether or not women who have been treated for breast cancer and in whom there is no evidence of active disease can be given HRT safely should they require it. The available data, such as they are, seem essentially reassuring, but most women and their doctors would probably prefer to err on the side of caution.[16] Evidence from randomised controlled trials would be helpful and such studies have been planned.

There is strong evidence that mammography is less sensitive and less specific in women receiving HRT than in other postmenopausal women as a conseqence of the increase in breast density in the former.[17] This observation has obvious implications for breast cancer screening programmes, especially as the prevalence of HRT use continues to rise.[18,19]

CONCLUSIONS

There is considerable evidence that the administration of stilboestrol to pregnant women and the administration of steroidal oestrogens (with or without progestogens), to prevent pregnancy or to relieve menopausal symptoms and prevent osteoporosis, produces a modest increase in the risk of breast cancer. The net effect of stilboestrol administration in pregnancy is clearly harmful and this treatment has not been used for two or more decades. Oral contraceptives and HRT, on the other hand, have a range of beneficial effects which have to be weighed up against the harmful effects in arriving at a balanced decision as to whether or not they should be used. In most circumstances the balance is in favour of oral contraceptive use, but there continues to be some uncertainty about the balance with respect to HRT.

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