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The pill and breast cancer: why the uncertainty?

So far over 20 epidemiological studies have looked for an association between oral contraceptives and subsequent breast cancer.¹ Their results have been broadly reassuring, though some uncertainty remains—particularly about young women using oral contraceptives. Today we publish (p 723) a case-control study from New Zealand that shows no association between the pill and breast cancer. This week, however, another study has been published in the *Swedish Medical Journal* showing an association between oral contraceptives and breast cancer, and we understand that this study will shortly be published again in an English language journal. What, then, are we to believe, and how should we advise our patients?

The pill has been widely used for long enough now to allow us to be reasonably certain that its use for family spacing—that is, after the first full term pregnancy—is not associated with any change in the risk of breast cancer. This conclusion (if true) is surprising because oral contraceptives reduce the risk of ovarian² and endometrial³ cancer—which, like breast cancer, are hormone dependent. Furthermore, oral contraceptives may increase the risk of cervical abnormalities.⁴ Epidemiologically it is thus difficult to understand why the breast is spared any effect—protective or otherwise—of the long term use of oral contraceptives. To the endocrinologist the lack of effect is less surprising: many hormones besides steroids interact to control mammary growth, and the role of local paracrine agents may be particularly important in regulating epithelial proliferation.^{5,6}

Concern about the pill and the breast is focusing on the safety of using oral contraceptives early in reproductive life, particularly before the first pregnancy. Some epidemiological studies suggest an association between “early” use and later breast cancer,^{7,8} while others do not.^{9,12} The two new reports add to our uncertainty. Why does a single study not give the definitive answer? The New Zealand report is a first rate epidemiological study and includes most of the cases of breast cancer presenting in New Zealand in the two years up to June 1985. Its methods are similar to those in other case-control studies, and it shows no overall increased risk with over 10 years’ use of oral contraceptives. In addition, it shows no increase in risk with long term use before the first pregnancy and before the age of 25. This conclusion is similar to that of the largest study ever to address this question, the cancer and steroid hormones (CASH) study from Atlanta.^{11,12} Both studies show only a suggestion of an increased risk of breast cancer at young age, but this might be because young women using oral contraceptives are more likely than those

not using oral contraceptives to have regular breast examinations: thus early diagnosis at a young age would be associated with using oral contraceptives.

The Swedish report also seems to be a first rate study. The number of women with breast cancer under the age of 45 is about twice that in the New Zealand study. (Women over that age probably had not used oral contraceptives long term when young.) Controls were tightly matched with cases both for age and for age at first full term pregnancy. The study finds an association between the long term use of oral contraceptives and risk of breast cancer that does not appear to be particularly associated with use before first pregnancy. There is a twofold increase in risk for women who have ever used oral contraceptives for eight or more years or for such a period before first pregnancy. If substantiated this finding would be very serious.

One possible reason for not accepting any current study as giving the final answer is that the use of oral contraceptives early in life may have a latent effect on the risk of breast cancer.¹³ If early use promotes precancerous changes that take time to progress into a tumour (which in turn takes time to be diagnosed) even recent studies may give misleading results.¹⁴ In Britain oral contraceptives became available in the early ’60s largely for married women but were not commonly prescribed to single women until the early ’70s. Thus only women born in the mid-’40s and later have been exposed in large numbers to long term use of oral contraceptives early in life. Such women have not yet reached the age of high risk for breast cancer, and insufficient time has elapsed to reject the possibility of a long latent effect. If the latent period were as long as 20 years¹⁵ and the true relative risk associated with use of oral contraceptives were as high as 3 the incidence of breast cancer in Britain would increase by around a fifth by the end of the century.¹⁶

Patterns of the use of oral contraceptives have varied appreciably with time in different countries. In Britain use early in life quickly became more common between 1970 and 1975, but in the USA a similar increase probably did not happen until the late ’70s.¹³ Such differences can give rise to predictable discrepancies between epidemiological studies,¹⁶ and to interpret studies conducted in the ’80s we ought to know in detail about prescribing patterns in the countries where they were done. This information is, however, difficult to find. If we knew that early use of oral contraceptives happened in Sweden much sooner than it did in New Zealand our interpretation of the current results would be pessimistic, but no such interpretation is possible on the

available data. The New Zealand study argues that in 1975 the rates of use of oral contraceptives were higher in that country than in Britain, but this does not necessarily apply to young women. By 1975 in Britain nearly 40% of sexually active single women aged under 20 were taking the pill,¹⁷ but it is not clear whether this was also true in New Zealand or Sweden.

Such data will, we hope, come from the controls in these various studies or from population surveys. We need to know not only the duration of early exposure to oral contraceptives but also the time that elapses between exposure and diagnosis. Tabulating relative risks by time since first use as these two studies have done is not enough. Nor is it helpful to standardise for duration of use of oral contraceptives as was done in the Swedish study: this might standardise out a possible latent effect. The duration of use and the time since first use are correlated with each other and with a possible latent period, but neither measures latency. A way to investigate a possible latent effect that overcomes these difficulties was described in 1981.¹⁸

Whether or not there is a latent effect of early use of oral contraceptives on breast cancer, there are other possible reasons for the discrepancy between these two studies. The Swedish study was conducted at a time of increasing consciousness of a possible association between the pill and breast cancer, and the cases and controls were fully aware of the purpose of the study at the time of their interview. The accuracy of recall of the use of oral contraceptives, going back 20 or more years, may not have been comparable between cases and controls. Women with breast cancer have strong reasons for thinking hard about their history; controls have not. Such differences can lead to serious bias in case-control studies—enough to explain a relative risk of 2.

On the other hand, the Swedish study matched the controls with cases very closely. In the New Zealand study the controls were not individually matched at all: adjustments were made in the analysis, and this may not be adequate when one is concerned with a rapidly changing exposure rate. In studies of this kind age is a crucial confounding variable because it influences not only the risk of breast cancer but also the risk of exposure to oral contraceptives. The popularity of oral contraceptives among young women has dramatically changed over a short time, and in current studies older women are much less likely than younger women to have been exposed to oral contraceptives at an early age.¹⁹ Because the patterns of pill use have changed so quickly adjustment within five year intervals, as was done in the New Zealand study, may be inadequate. In the Swedish study controls were the same age as each case to within a single month. Age at first birth is another important confounding variable, and in the Swedish study some controls had their first baby within two months of the corresponding case.

Finally, the types of pill used by the women in these studies may have varied. Oral contraceptive formulations vary with time and place, and the dosages of synthetic hormones have decreased appreciably over the past 20 years. If oral contraceptives are implicated in the risk of breast cancer their effect may be altered by hormone and dose as well as by duration of use and the woman's age at use. Neither of the new studies gives any indication of the types of pill used, and therefore we have no idea whether the results are relevant to our own current practice.

Nevertheless, the fact that one of these studies shows a possible association of oral contraceptives with breast cancer provides a powerful reason for trying to find out more.

Epidemiology may be a blunt tool for dissecting this complicated relation and needs to be complemented by a much better understanding of the biological effects of hormones on breast tissue.^{20,21} Some of the outstanding questions could be investigated by collaboration between investigators with open minds. Until that happens and until other studies under way are reported the question remains open. We cannot say with any certainty that the pill used for long periods early in reproductive life is, or is not, associated with a change in the risk of breast cancer. While this uncertainty remains there is no reason to change our prescribing habits or our advice to women using the pill.

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Arthroscopic surgery of the knee

Just as the surgical replacement of joints has changed the practice of orthopaedic surgery in general, so arthroscopy has changed the character of knee surgery in particular. The lead came from surgeons in Japan in the 1960s, but interest in arthroscopy quickly spread to other countries.^{1,3} As surgeons gained experience of diagnostic arthroscopy those with a special interest in knee surgery began to devise ways of developing the arthroscope to enable them to carry out procedures within the joint. In England Dandy has pioneered these methods, which are steadily becoming established in specialist units.⁴