Ovarian cancer family and prophylactic choices

D G R Evans, G Ribiero, D Warrell, D Donnai

Abstract
A subject from a family with ovarian cancer who has developed bilateral medullary carcinoma of the breast at the age of 40 is presented. The family is consistent with dominant inheritance of ovarian cancer and 12 female family members at 12.5%, 25%, and 50% risk, including our case, have undergone bilateral prophylactic oophorectomy and been given hormone replacement therapy. Despite the risk of further primary tumours of the breast our patient chose to have treatment with wide excision and radiotherapy. The implications for screening, prophylaxis, and hormone replacement therapy for this family are discussed.

Familial ovarian cancer is now a well described entity. There have been around 40 reports of familial aggregations, many of which are consistent with an autosomal dominant mode of inheritance.1 There have been even more reports suggesting dominant inheritance of breast cancer2-3 and others combining the two.

Case report
A 40 year old woman (IV.32, figure) from a family where seven women had developed ovarian cancer presented with a breast lump two years after hysterectomy and bilateral prophylactic oophorectomy. Family members had previously been extensively studied and counselled. Five cases of histologically proven ovarian cancer and two further cases from history and death certification were found (table). Subjects were identified at 12.5%, 25%, and 50% risk. At the time of this report 12 subjects have undergone prophylactic oophorectomy and been given hormone replacement therapy with premarin 1.25 mg per day. Our patient had been given a 50% risk of tumour sites.4 Formerly, when screening techniques for ovarian cancer were inadequate, prophylactic oophorectomy was widely proposed. Mastectomy for those at risk of breast cancer is a far less popular preventive measure in this country. We present a woman from an apparently dominant ovarian cancer family who opted for oophorectomy and later developed breast cancer.

Family pedigree showing dominant inheritance of cancer risk.
developing the disease. The breast lump had been discovered during self-examination which the patient practised at regular intervals, but was not detected by mammography. At operation, however, a well circumscribed tumour was identified and removed. Histologically it was an atypical medullary carcinoma, with no axillary node involvement. The patient underwent a 20 day course of radiotherapy and was started on tamoxifen 20 mg daily. Three months after discovery of the lump in her right breast, a similar lesion was detected on the left side. In view of her family history and the bilateral disease she was offered a mastectomy, because of the high risk of a further primary tumour. However, she opted for a wide excision again. She remained happy with her decision postoperatively. Although she had chosen oophorectomy because of the risk of ovarian cancer, she stated that mastectomy was not acceptable as her breasts were more a part of her perceived body image. There were also extenuating personal circumstances which made a conservative operation preferable.

Discussion
There have been many reports of familial aggregation since the first report of familial ovarian cancer. The tumours are indistinguishable from sporadic cases on histology and are usually papillary serous adenocarcinoma. The association of ovarian and breast cancer in families and in case control studies has also been noted. Medullary cancer of the breast is an uncommon tumour type and is usually associated with a good prognosis. One report concluded that bilaterality is common and is likely to be associated with a family history. The same report noted that 56% of associated carcinomas occurred in the ovaries. Medullary carcinoma of the breast has also been reported in ovarian cancer families.

The family reported here clearly shows a pattern of susceptibility to ovarian cancer consistent with dominant transmission. In keeping with patients in previous reports, a large number of the relatives at risk have opted for bilateral oophorectomy. The possible risk of breast cancer was not discussed, as it had not previously occurred in this large pedigree. The onset of bilateral medullary breast cancer in a subject at 50% risk of ovarian cancer is highly suggestive that she carries the same cancer gene which caused ovarian malignancy in her mother. The fact that mammography failed to detect this tumour poses a number of problems. Firstly, the index case is at risk of future primary breast tumours as most of her breasts were conserved. Secondly, other family members at 50% risk may want to have some form of breast screening. An option which has been chosen by the family has been to combine ultrasound and mammography to detect early tumours. As the majority of subjects at risk are effectively postmenopausal owing to oophorectomy, the usual drawback of interpretation of a highly glandular breast on the radiograph does not hold. Therefore, screening from 35 years has been offered to the family. The role of oestrogen replacement therapy (ERT) in these women does need examining. Prolonged use of 20 years duration is associated with a relative risk of developing breast cancer of 1.5 to 2.0 in the general population. Shorter usage, for example five years, has not been proven to increase risk. However, the protective effect of oophorectomy would be expected to outweigh that of a short duration of ERT. Decisions about replacement treatment also have to be made taking into account quality of life and the beneficial effects on the skeletal and cardiovascular system. A compromise may be to treat with the lowest dose of ERT which prevents symptoms and if possible to limit long term usage.

Although it would seem logical to offer the option of bilateral mastectomy to a woman from a dominant breast cancer family who develops their first primary, in our experience women are far more likely to agree to losing their ovaries, even when at only 25% risk, than they are to having a prophylactic mastectomy. We are aware of only three women from over 250 families with a history of breast cancer who have opted for mastectomy. This contrasts with 14 cases from five families with ovarian cancer who have had prophylactic oophorectomy. Indeed a further woman (IV.22) is awaiting the operation. A previous study reported 28 women from 15 families who chose to have oophorectomy.

There has been little further evidence on the risk of post-oophorectomy intra-abdominal malignancy in ovarian cancer families since it was first reported. This may well represent a much lower incidence of this complication than was anticipated. It will be necessary to study a large number of families such as ours to determine the true likelihood of this almost universally fatal malignancy. Without such information it is difficult to counsel women who are considering oophorectomy accurately.

Until a subject opts for oophorectomy, or if they do not, some form of screening should be offered. Pelvic bimanual examination is a poor technique compared to abdominal ultrasound as it identifies the ovaries in only 30% of cases. Even abdominal ultrasound cannot identify the ovaries in 8 to 13% of subjects at risk, especially when they are overweight. Furthermore, even in a specialist centre, up to 66 women may have a false positive result for every cancer identified. These problems can be reduced significantly by using vaginal probes in combination with doppler colour flow imaging. The vaginal approach is more likely to identify the ovaries and the doppler to
distinguish between benign and malignant disease. Although numbers detected so far are small, sensitivity is around 100% and this would therefore be the preferred screening test in women at risk where it is available. Biochemical markers such as CA 125 are unlikely to be helpful when the definitive tests are used, owing to their low specificity, but may be of value in combination with abdominal ultrasound.

In summary, women from ovarian cancer families should be counselled about their risk of developing the disease and offered annual vaginal ultrasound screening from 25 years old, or five years before the earliest cancer in the family.

For those at high risk the option of bilateral oophorectomy after reproduction should be discussed. The possible risk of a peritoneal cancer, despite this measure, may need to be mentioned. The fact that there may also be an increased risk of breast cancer even if this has not occurred in the family may also need to be discussed together with options for screening. The identification of the gene or genes responsible for familial aggregations will greatly alter our current practice and the options for family members.

Note added in proof
Since writing this article, a further subject has developed bilateral breast cancer (IV.23).