Aims: To investigate the effect of age at onset and genetic factors on prognosis in young onset breast cancer.

Background: Breast cancer in women is a common disease. Less than 5% of cases are diagnosed before 40 years of age. Young age at diagnosis is associated with a worse prognosis so there are likely to be fundamental biological differences in the young onset group. Less than 5% of all breast cancer cases are likely to be secondary to the presence of the high risk genes BRCA1 or BRCA2, but a higher proportion of women affected at young ages have a genetic predisposition to the disease. The POSH study was established in order to be able to investigate the prognostic implications of genetic status, including tumour biology and treatment outcomes in individuals with a genetic predisposition to breast cancer due to one of the known high risk genes compared to those with no obvious predisposition (MREC 00/6/69). 2000 women had been recruited by July 2006 and a further 1000 will be recruited by the end of the recruiting period, December 2007.

Age at onset younger than 35 has been associated with poor prognosis compared to older onset cases (1). Full histopathology reports are available now for over 1000 cases and this preliminary analysis looks at reported histopathological characteristics of tumours arising in very young onset cases (<35 years at diagnosis) compared with those with age at onset 36-40 years. We decided to look at the prognostic characteristics of tumour arising around this clinically observed age cut off to assess whether tumour biology was different in the younger age group. We also examined whether a family history of breast cancer altered treatment choices or short term outcomes.

Methods: The POSH study is a prospective cohort study of young onset breast cancer patients diagnosed between January 2001 and June 2006. Patients meeting the eligibility criteria are recruited from participating centres across the UK and followed prospectively. Data collected about family history, demographic data and data detailing diagnosis and treatment as well as annual follow up is in progress.

We reviewed the pathology reports from the first 1,180 recruits where reports were sent to the study centre and in whom family history questionnairenaires had been completed. Recruits were divided into two age groups; very young aged (<35 year at diagnosis) and young (36-40 years at diagnosis) and into 4 groups on the basis of ranking of genetic risk by commercially available software (Cyrillic®).

Two thirds (66%) of individuals had no family history of breast or ovarian cancer, the remainder divided roughly equally between the single familial categories (Groups 1-4) with the highest category (Group 4) being those patients either known or very likely to carry a BRCA1 or BRCA2 gene mutation (figure 1).

Results: Data on survival for 1180 cases were analysed. The overall median follow up time was 20 months. Relapse free survival was significantly poorer in the very young onset group (= 6.739, p = 0.009) (Figure 2). This is likely to be explained by more aggressive tumour biology; grade 3, ER negative tumours were significantly more common in the very young age group 171/494 (35%) compared to the 36-40 year age group 179/710 (25%) (p<0.001). PR positive cases were also less frequent in the younger age group (177/355) compared with the older age group (301/497) (p<0.01). The choice of primary surgery (mastectomy versus breast conservation) did not differ by age group, roughly half of all patients had breast conserving treatment in each age group.

When the family history is taken into account, higher tumour grade and decreasing tumour size were observed as the strength of the family history increased through Groups 1-4 (figures 4a and 4b). An increasing likelihood of being treated by mastectomy was also observed with increasing strength of family history reported. In contrast to much of the recent literature based on retrospective reports, our results are consistent with a more typical age group with breast cancer who had mastectomy as the primary treatment. This is likely to be reflected by the fact that the young age group may be responsible for the early relapses observed here at 20 months median follow up. Further follow up will determine if this will later be matched by the more steady rate of relapse observed in ER -ve tumours as seen in a more typical age group.

Discussion: These data confirm the observations by others of more aggressive tumour phenotype in patients diagnosed at very young ages with breast cancer and in patients with a strong family history of the disease. Although we observed a significantly worse outlook in the short term for very young age groups, no significant difference was observed in hereditary breast cancer cases in contrast to much of the recent literature based on retrospective series. The preponderance of ER -ve tumours in the very young group may be responsible for the early relapses observed here at 20 months median follow up. Further follow up will determine if this will later be matched by the more steady rate of relapse observed in ER -ve tumours as seen in a more typical age group.

Although we did not observe a clearly worse outcome associated with hereditary breast cancer, it should be remembered that risk reducing surgery in women known or suspected hereditary breast cancer should be a secondary consideration to adequate management of the presenting primary tumour.

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