

Prospective study of Outcomes in Sporadic versus Hereditary breast cancer

Summary

There is emerging evidence of fundamental pathobiological differences in breast cancers arising on a background of hereditary predisposition suggesting that hereditary breast cancers may behave differently in terms of their phenotype, prognosis and response to treatment. These observed differences lead to uncertainty as to the treatment advice that should be offered to women with proven or suspected hereditary breast cancer. The only published studies are retrospective and the results are conflicting due to biased ascertainment, inappropriate controls and incomplete data. The window of opportunity in which to conduct the proposed cohort study is small but it is vital that the study is done in order to define precisely the natural history of breast cancer in known mutation carriers compared to that observed in non-hereditary cases. This study is designed to give more accurate information to guide clinical decisions. The collection of genomic DNA coupled with meticulous documentation of clinical details and systematic pathological review will also provide an invaluable resource for addressing future questions as further cancer susceptibility genes are identified.

The principal research questions

- (i) Is there any difference in survival for sporadic versus hereditary cases matched for conventional prognostic factors and treatment modality?
- (ii) Is there a difference in local recurrence risk after breast conserving treatment for women with early breast cancer in hereditary versus sporadic cases?
- (iii) Is there a difference in contralateral breast cancer occurrence in hereditary versus sporadic cases?

Why now?

Technology and cost currently limit the ability to perform rapid molecular genetic testing. Thus most newly diagnosed breast cancer cases will be treated in a conventional manner regardless of their genetic status. As technology moves on and genetic testing becomes more readily available, treatment decisions may be increasingly influenced by knowledge of the patient's genetic make-up, based on unreliable information from small, flawed retrospective studies. Understanding the inherent prognosis related to genetic status is essential before treatments can be preferentially advised on the basis of that genetic status.

Study design

A large, well designed prospective cohort study is required in order to address the principle study question adequately. A total of 3,000 consecutive incident breast cancer cases diagnosed under 40 years of age from the UK will be recruited into the study. Pedigree analysis and molecular genetic analysis will allow construction of the following sub-groups from this cohort for a nested case-control study:-

- BRCA1 gene carriers
- BRCA2 gene carriers
- BRCAother
- No relevant family history and no detectable gene mutation

Outcome measures

<i>Primary</i>	Survival (relapse free and overall at 2, 5 and 10 years)
<i>Secondary</i>	incidence and clinical features of ipsilateral recurrence
	incidence of contralateral breast cancer (at 2, 5 and 10 years)
	histopathology subgroup analysis (centralised pathology review)

adjuvant treatment outcomes - effect on new/recurrent disease
prophylactic surgery outcomes - effect on relapse free and overall survival with
mastectomy or oophorectomy.

Data collection

Initial data collection at recruitment followed by a 6 month check for completeness and clinical follow up annually thereafter

Sample size and power calculations

The proposed study group of at least 2,000 women diagnosed with breast cancer age ≤ 40 years will contain an estimated 200 BRCA1 gene carriers (10%), perhaps 100 BRCA2 gene carriers (5%) and some 600 additional women with a significant family history of breast cancer who are likely to carry some other genetic predisposition (BRCAother). These estimates are based on a number of published molecular analyses in cohorts of breast cancer patients and from segregation analyses. This number of recruits will give an 80% power to detect a 7% difference in survival between “hereditary” cases compared with matched “control” (sporadic) cases.

Statistical analysis

An interim analysis will be carried out to check rate of recruitment and after the first full year of molecular analysis (proposed start time for this is year 2 of the study) we will assess the proportion of recruits showing a BRCA1 or BRCA2 mutation. Review of power calculations at that stage may require some adjustment of recruitment targets if the number of gene carriers is fewer than expected.

Are there any planned sub-group analyses?

We plan to compare the outcomes in two defined genetic risk groups (BRCA1 and BRCA2) with the outcome in the fourth group who appear to have sporadic breast cancer. Future definition of discrete genetic groups for comparison with controls will depend on the discovery and analysis of new breast cancer genes.

TRIAL MANAGEMENT

The study steering group will review study progress, data collection, and comment on any proposed add-on studies. In addition all will ensure good UK-wide recruitment from collaborating centers. Data and DNA will be collected and stored in the Cancer Sciences Research Division of the University of Southampton. Data analysis will take place in Southampton or Oxford under the supervision of Professor Doug Altman.