BRCA1/2 negative status predicts no extended risk of invasive ovarian cancer

References

Ovarian cancer among 8005 women from a breast cancer family history clinic: no increased risk of invasive ovarian cancer in families testing negative for BRCA1 and BRCA2

Since the association of BRCA1 and BRCA2 mutations with enhanced breast cancer risk, debate has continued whether these mutations also affect ovarian cancer risk. Genetic testing has confirmed an increased baseline risk for ovarian cancer in carriers of BRCA1/2 mutations. Several studies reveal a cumulative mutation risk for developing ovarian cancer in carriers of mutations in BRCA1 is approximately 35% and that for BRCA2 is approximately 25% (1). However, an important question, especially for genetic counseling is whether families with breast cancer history, testing negative for BRCA1/2 have elevated risk of developing ovarian cancer. There have been three studies so far addressing this issue with variable conclusions. One of these studies found an enhanced incidence ratio of ovarian cancer in families without BRCA1/2 mutations, whereas the other studies found no increase in incidence of ovarian cancer in BRCA1/2 negative families (2). The varying findings from these studies and the recent identification of two other genes contributing towards an increased risk of breast and ovarian cancer have prompted a reassessment of risk association for ovarian cancer in BRCA negative families.

To address these questions, Ingham et al. designed a long term prospective study and assessed the risk of invasive ovarian cancer in 8005 women from 895 families including 1613 women who tested negative for BRCA1/2 mutations. The cohorts were from The Breast Cancer Family History Clinic (FHC), Manchester. Family trees of all first, second and whenever available, third degree relatives from referrals and attending patients at the clinic were available. Mutation
status for BRCA1/2 in tested cases was recorded and all information was stored in a database. Data on ovarian cancer incidences were recorded from the North West Cancer Intelligence Service (NW CIS) and confirmed from the hospital pathology records or death certification prospectively. Exclusion criteria were pre-existing ovarian cancer or oophorectomy prior to referral. Mutation status was evaluated using sequencing and multiple ligation dependent probe amplification (MLPA) or combination of conformation sensitive gel electrophoresis in 86 fragments and MLPA.

Analyses to determine person-years at risk of ovarian cancer for each family’s genetic status were performed using population level data. The relative risk (RR) calculations were determined by dividing the observed risk of developing ovarian cancers by the expected risk from the general population. The analysis revealed a 50 RR for invasive epithelial ovarian tumors in BRCA1 positive subjects and a 16.67 RR in BRCA2 positive subjects. BRCA status did not affect borderline tumor risk, which was found to be zero in both BRCA1 and BRCA2 positive cases. Cumulative ovarian cancer risk for BRCA1 positive cases was high at 44.83 and that for BRCA2 was 15.15. Interestingly, for BRCA negative cases, the observed risk of invasive ovarian cancer fell below that of the expected population risk at an RR of 0.37, whereas the borderline tumor incidence was nearly eight times as much as the expected general population risk (Fig. 2). These data reveal a strong association of BRCA positive status and invasive ovarian cancers, but not borderline cancers.

Additionally, the authors also computed the lifetime breast cancer risk using the Tyrer–Cuzick model. Analyses revealed significant differences in BRCA negative and BRCA untested families. Interestingly, 60% BRCA negative families were classified as high risk (lifetime risk greater than one in four) before family testing, whereas n untested families only 34% were classified as such high risk. For ovarian cancers, 80% tested positive as index case. Three cases tested negative for BRCA1/2, of which, two had borderline tumours and one had developed this after developing breast cancer.

The findings presented in this study are important as BRCA1/2 mutations account for most of the inherited link between breast and ovarian cancers. The major determining factor in excluding the risk of ovarian cancer in families testing negative for BRCA1/2 is the sensitivity of the test (Fig. 2). Currently available testing methods are limited in their sensitivity as they do not screen for intronic regions, phenocopy and positional effects. This study was also complicated by follow-up dropouts, relocation and testing sensitivity. However, the large numbers and long-follow up years present a fair estimate for ovarian cancer risk associated with BRCA status and is reassuring for breast cancer only cases testing negative for BRCA1/2 that their risk of developing invasive ovarian cancer has not increased. Finally, this is the largest prospective follow-up study which demonstrates that there is no clinically significant increase in risk of invasive ovarian cancer in families testing negative for BRCA1/2.

JV Patankar
Department of Medical Genetics, Centre for Molecular Medicine and Therapeutics, University of British Columbia, 950 West 28th Avenue, Vancouver, British Columbia, V5Z4H4, Canada
e-mail: jpatankar@cmmt.ubc.ca

Fig. 2. Incidence of invasive epithelial ovarian cancer.