Breast and ovarian cancer risks to carriers of the BRCA1 5382insC and 185delAG and BRCA2 6174delT mutations: a combined analysis of 22 population based studies


A recent report estimated the breast cancer risks in carriers of the three Ashkenazi founder mutations to be higher than previously published estimates derived from population based studies. In an attempt to confirm this, the breast and ovarian cancer risks associated with the three Ashkenazi founder mutations were estimated using families included in a previous meta-analysis of population based studies. The estimated breast cancer risks for each of the founder BRCA1 and BRCA2 mutations were similar to the corresponding estimates based on all BRCA1 or BRCA2 mutations in the meta-analysis. These estimates appear to be consistent with the observed prevalence of the mutations in the Ashkenazi Jewish population.

We recently reported the average risks of breast and ovarian cancer associated with BRCA1 and BRCA2 mutations, using a meta-analysis of pedigree data from 498 BRCA1 and BRCA2 mutation carriers identified through population based studies of women with breast and ovarian cancer.1 King et al2 estimated the risks to carriers in the three Ashkenazi founder mutations (BRCA1 185delAG and 5382insC, and BRCA2 6174delT) by genotyping the relatives of 104 mutation carriers. They concluded that the risks are higher than both our estimates or other previously published estimates.3–6 To provide a more direct comparison between the two studies, we estimated the breast and ovarian cancer risks associated with the three Ashkenazi founder mutations using families included in our meta-analysis.

Among the index cases studied by Antoniou et al,7 75 were BRCA1 185delAG carriers, 69 were BRCA1 5382insC carriers, and 52 were BRCA2 6174delT carriers. Sixty three (84%) of the 185delAG mutation carriers and 42 (81%) of the 6174delT mutation carriers were identified through studies of Ashkenazi Jewish populations. However, only 22 (32%) of

Table 1

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>185 del AG</th>
<th>5382insC</th>
<th>6174delT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Breast cancer</td>
<td>Ovarian cancer</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>40</td>
<td>10 (3 to 18)</td>
<td>3 (0 to 7)</td>
<td>14 (5 to 23)</td>
</tr>
<tr>
<td>50</td>
<td>27 (13 to 38)</td>
<td>11 (2 to 19)</td>
<td>46 (29 to 59)</td>
</tr>
<tr>
<td>60</td>
<td>47 (26 to 62)</td>
<td>14 (2 to 24)</td>
<td>57 (35 to 72)</td>
</tr>
<tr>
<td>70</td>
<td>64 (34 to 80)</td>
<td>14 (2 to 24)</td>
<td>67 (36 to 83)</td>
</tr>
</tbody>
</table>

CI, confidence interval.

The 95% confidence intervals for the estimated breast cancer cumulative risks in BRCA2 mutation carriers exclude the corresponding point estimates of King et al2 at all ages. Our lower estimate is more consistent with estimates obtained by other studies.3 The difference in risks between BRCA1 and BRCA2 carriers also appears more consistent with the observed prevalence of the founder mutations among breast cancer cases in the Ashkenazi Jewish population.

Our estimated breast cancer risks for the Ashkenazi founder mutations were similar to the estimates obtained

This article is available free on JMG online via the JMG Unlocked open access trial, funded by the Joint Information Systems Committee. For further information, see http://jmg.bmjournals.com/cgi/content/full/42/2/97
from our meta-analysis of population based studies for all BRCA1 and BRCA2 mutations combined. The ovarian cancer risks in 6174delT carriers were somewhat higher than the average BRCA2 risks (20% v 11%), consistent with the observation that mutations within the ovarian cancer cluster region are associated with a higher ovarian cancer risk. The ovarian cancer risk in carriers of the 185delAG mutation is lower than expected, but the confidence limits are wide. Moreover, the risks conferred by this mutation are not significantly different from the risks conferred by 5382insC (p = 0.53). Given the much larger number of families studied, the overall estimates of Antoniou et al. probably provide a more reliable basis for risk assessment for carriers of BRCA1 and BRCA2 mutations identified through population studies than estimates based on individual mutations.

ACKNOWLEDGEMENTS
These analyses were supported by Cancer Research UK (formerly Cancer Research Campaign) and National Institutes of Health (NIH) grant 1R01 CA81203. DFE is a principal research fellow of Cancer Research UK, and PDPP is a senior clinical research fellow of Cancer Research Campaign (formerly Cancer Research Campaign) and National Institutes of Health (NIH) grant 1R01 CA81203. A C Antoniou*, D Thompson, C Evans, D F Easton, Cancer Research U.K. Genetic Epidemiology Unit, Department of Public Health, University of Cambridge, Cambridge, UK

P D P Pharoah*, Cancer Research UK Human Genetics Group, Department of Oncology, University of Cambridge
S Narod, E Warmer, Centre for Research on Women’s Health, University of Toronto, Toronto, Canada
H A Risch, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut, USA
H Tulinius, S Thorlacius, Icelandic Cancer Society, Reykjavik, Iceland
J E Eyfjord, University of Iceland, Reykjavik
J L Hopper, Centre for Genetic Epidemiology, Department of Public Health, The University of Melbourne, Melbourne, Australia
H Olsson, O Johansson, A Borg, Department of Oncology, Jubilee Institute, Lund University Hospital, Lund, Sweden
B Pasini, S Manoukian, National Cancer Institute, Milan, Italy
P Radice, FIRC Institute of Molecular Oncology, Milan
D M Eccles, Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton, UK
N Tong, Department of Chemical Pathology, The Chinese University of Hong Kong, Republic of China
E Olah, National Institute of Oncology, Budapest, Hungary
H Anton-Culver, Epidemiology Division, Department of Medicine, University of California, Irvine, California, USA
J Lubinski, J Gronwald, B Gorski, Hereditary Cancer Centre, Department of Genetics and Pathology, Pomeranian Academy of Medicine, Szczecin, Poland
H Nevalinna, Departments of Obstetrics and Gynaecology, Helsinki University Central Hospital, Helsinki, Finland
H Eerola, Departments of Oncology, Helsinki University Central Hospital, Helsinki
K Syrjakoski, O-P Kallioniemi, laboratory of Cancer Genetics, Institute of Medical Technology, Tampere University and Tampere University Hospital, Tampere, Finland
J Peto, Section of Epidemiology, Institute of Cancer Research, Sutton, Surrey, UK
F Lalloo, D G Evans, Academic Unit of Medical Genetics and Regional Genetics Service, St Mary’s Hospital, Manchester, UK

The first two authors contributed equally to this work.

Competing interests: none declared

Correspondence to: Dr Douglas F Easton, Cancer Research UK Genetic Epidemiology Unit, Strangeways Research Laboratory, Worts Causeway, Cambridge CB1 8RN, UK; doug.easton@srl.cam.ac.uk

Received 16 June 2004
Revised version received 23 July 2004
Accepted for publication 28 July 2004

REFERENCES

www.jmedgenet.com