Carrier risk status changes resulting from mutation testing in hereditary non-polyposis colorectal cancer and hereditary breast-ovarian cancer

P Watson, S A Narod, R Fodde, A Wagner, J F Lynch, S T Tinley, C L Snyder, S A Coronel, B Riley, Y Kinarsky, H T Lynch

Context: In hereditary cancer syndrome families with an identified cancer associated mutation, mutation testing changes the carrier risk status of the tested person and may change the carrier risk status of relatives.

Objective: This study aimed to describe the change in the distribution of carrier risk status resulting from testing in hereditary breast-ovarian cancer (HBOC) and hereditary non-polyposis colorectal cancer (HNPPC) families.

Design: This was an observational cohort study.

Patients: The cohort included members of 75 HBOC and 47 HNPCC families. Of the 10 910 cohort members, 1 408 were tested for a mutation and learned their test results.

Outcome measure: Carrier risk for all cohort members was assessed before and after mutation testing.

Results: There was a change in carrier risk status in 2906 subjects after testing of 1 408 family members. The most common type of carrier risk change, from at risk to non-carrier status, accounted for 77% of the risk changes; 12% were a change to known carrier status from a lower risk. Sixty percent of persons with a carrier risk status change were not themselves tested; their risk status changed because of a relative’s test result.

Conclusions: Carrier risk status changes from uncertainty to certainty (that is, to carrier or to non-carrier) account for 89% of risk changes resulting from testing. These risk changes affect cancer prevention recommendations, most commonly reducing their burden. Current practices do not ensure that untested family members are informed about changes in their carrier risk status which result from mutation testing of their relatives.
they may undergo unnecessary cancer screening or prophylactic surgery, adding to the pressure on scarce medical resources.

These are precisely the problems that mutation testing is supposed to address. However, the actual changes in carrier risk for tested and untested family members following mutation testing, in the clinical practice setting, have not yet been fully described. Our purpose is to show quantitative changes in carrier risk distribution which have resulted from genetic testing in HNPCC and HBOC families. Note that our focus is on carrier risk, not risk for cancer. Tested non-carriers of the family’s deleterious mutations are at virtually zero carrier risk but still at the general population risk for developing a phenotype cancer, while tested carriers are at virtually 100% carrier risk but (because of incomplete penetrance) at less than 100% risk of developing a cancer syndrome.

METHODS
This study has been approved by Creighton University’s Institutional Review Board. We have included all HNPCC and HBOC families from Creighton’s cancer family resource in which at least one family member has been found to carry a specific cancer causing mutation (BRCA1 or BRCA2 in HBOC, and MSH2 or MLH1 in HNPCC), and has been informed of the test result in the context of genetic counselling.

Within these families, we identified the progenitors (Table 1). All of the descendants of the progenitors, however distant, were included in the studied cohort. Each cohort member was assigned a cancer based carrier risk, mutation test based carrier risk, and final carrier risk as summarised in Table 2. All known cancer diagnoses, and all disclosed mutation test results, were used in risk assessments, regardless of the vital status or age of the tested/diagnosed person. A schematic pedigree, illustrating cancer based, mutation based, and final carrier risk assignment, is shown in Fig 1. Counts of subjects in carrier risk categories were made, along with counts of subjects with various types of carrier risk changes (differences between cancer based and final carrier risk). Family members were included in these counts if they were progenitor descendants, alive, and over the age of 18 at the time of this study.

RESULTS
The studied cohort included 75 HBOC and 47 HNPCC families. The 10 910 living, adult, at risk members of these families included in the study were nearly evenly divided between HNPCC and HBOC family members (51.0% HNPCC). There was an even sex distribution (50.4% female in HBOC, 50.5% female in HNPCC). The average age of these subjects at the time of the study was 43.2 in HBOC and 43.0 in HNPCC (overall range 18-99). A total of 1408 persons (678 from HNPCC families, 730 from HBOC families) were tested and had genetic counselling in which their test results were disclosed to them. Overall, 59% of mutation tests were negative (57% in HBOC, 60% in HNPCC). The proportion of negative tests in each of the cancer based carrier risk groups were as follows: 8% of 239 tests in 100% risk group, 64% of 813 tests of 50% risk group, 84% of 290 tests of 25% risk group, and 91% of 46 tests of low risk group.

This resulted in a change in carrier risk status in 2906 persons (table 3) The majority (2237 persons or 77% of 2906) had their carrier risk changed to 0%, either because they personally had a negative mutation test, or because their parent or grandparent had a negative mutation test, from which we could infer that this case was also a non-carrier (fig 1). This count includes 22 persons who had a prior (cancer based) carrier risk of 100%. Since these persons were proven by test not to carry the mutation shared by most affected family members, they were judged to be sporadic cancer cases (phenocopies). The next most common type of change was a change to 100% carrier risk: 348 persons (12% of 2906) had a cancer based carrier risk of low, 25%, or 50%, and were changed as a result of mutation testing to a final carrier risk of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Definitions for inclusion rules and carrier risk classification rules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progenitor, HNPCC family</td>
<td>The closest common ancestors of all mutation carriers by test, plus cases with any of the following: endometrial cancer age &lt;50, colon cancer age &lt;50, multiple colon/ovarian cancer</td>
</tr>
<tr>
<td>Progenitor, HBOC family</td>
<td>The closest common ancestors of all mutation carriers by test plus cases with any of the following: breast cancer age &lt;50, ovarian cancer any age, or multiple breast/ovary cancer</td>
</tr>
<tr>
<td>HNPCC cancer</td>
<td>Invasive cancer of the colon, endometrium, ovary, stomach, or small bowel, or an invasive transitional cell carcinoma of the kidney or ureter</td>
</tr>
<tr>
<td>HBOC cancer</td>
<td>Invasive cancer of the breast or ovary</td>
</tr>
<tr>
<td>Known carrier</td>
<td>A direct test for a specific mutation, previously identified in other family members, was positive and results were disclosed</td>
</tr>
<tr>
<td>Known non-carrier</td>
<td>A direct test for a specific mutation, previously identified in other family members, was negative and results were disclosed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Carrier risk classification among the descendants of progenitors.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer based carrier risk: All descendants of progenitors are classified, and mutation test results are ignored</td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>Affected with any syndrome cancer (see definitions) or having a descendant affected with a syndrome cancer</td>
</tr>
<tr>
<td>50%</td>
<td>Having a first degree relative with cancer based carrier risk=100%</td>
</tr>
<tr>
<td>25%</td>
<td>Having a first degree relative with cancer based carrier risk=50%</td>
</tr>
<tr>
<td>Low</td>
<td>All other family members descended from the progenitors</td>
</tr>
<tr>
<td>Mutation test based risk: Only family members in branches with tested mutation carriers are classified</td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>Being a known non-carrier (see definitions) or an inferred non-carrier (based on known non-carrier ancestors)</td>
</tr>
<tr>
<td>100%</td>
<td>Being a known carrier (see definitions) or an inferred carrier (based on known carrier descendants)</td>
</tr>
<tr>
<td>50%</td>
<td>Having a first degree relative with mutation test based carrier risk=100%</td>
</tr>
<tr>
<td>25%</td>
<td>Having a first degree relative with mutation test based carrier risk=50%</td>
</tr>
<tr>
<td>Low</td>
<td>Any other member of the family in a branch with some mutation tested positive cases</td>
</tr>
</tbody>
</table>

All systems of risk classification aim to quantitate risk of carrying an HNPCC or HBOC associated mutation. A person is assigned to the first (as listed) appropriate risk category for cancer based and mutation test based risk. Final carrier risk was equal to the higher of the two values (cancer based risk and mutation based risk), except when mutation based risk was zero, in which case final risk was zero. All descendants of progenitors were assigned a final carrier risk.
In some cases this change occurred because of their own positive mutation test result, and in other cases because of the positive test result of a descendant, from which we could infer that this case was also a carrier (fig 1). The remaining 321 carrier risk changes (11% of 2906) involved changing from low or 25% risk to 50% risk, or from low risk to 25% risk. All such changes occurred because of a positive test result in another family member (fig 1).

Of the 1408 mutation tests included in this study, 237 resulted in no change in carrier risk status. These were positive mutation tests of persons with a pre-testing (cancer based) carrier risk of 100%. In these cases, carrier status was confirmed by mutation testing. An additional 24 persons with cancer based carrier risk of 100% had their carrier status confirmed by inference from a positive mutation test in a relative (fig 1). The pre- and post-mutation testing distribution of risk in the entire cohort of 10 910 family members is shown in fig 2.

This cohort included 5342 HBOC and 5568 HNPCC family members. The distribution of carrier risk status changes was very similar in the two subsets (tables 4 and 5).

Table 3 Number of cases in each final carrier risk class, broken down by original (cancer based) risk class, including both HBOC and HNPCC family members.

<table>
<thead>
<tr>
<th>Cancer based carrier risk</th>
<th>Final carrier risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Low</td>
<td>771</td>
</tr>
<tr>
<td>25%</td>
<td>894</td>
</tr>
<tr>
<td>50%</td>
<td>550</td>
</tr>
<tr>
<td>100%</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>2237</td>
</tr>
</tbody>
</table>

The off diagonal values (bold) comprise the 2906 cases of change in carrier risk status as a result of mutation test result disclosure. Note that of the 441 classified as cancer based risk=final risk=100, 265 were tested or inferred carriers based on mutation test results, while in the remaining 176 cases' final risk was based on cancer status only.

Figure 1 An illustration of the application of rules for assigning carrier risk based on cancer family history and mutation test results in an HNPCC family. Note that in all these cases except one (colon cancer in generation III), since mutation test based carrier risk is either zero, equal to, or higher than the cancer based carrier risk, final carrier risk will equal mutation test based risk. When mutation test based carrier risk was greater than zero but less than the cancer based carrier risk, final risk was equal to cancer based carrier risk. Note that cancer based carrier risk for each family member is based entirely on degree of relationship to the most nearly related of the family members with a syndrome cancer, under the assumption that all syndrome cancers occur in persons with a mutation which is identical by descent. Mutation test based risk is based entirely on the degree of relation to tested carriers, under the assumption that only one mutation is of interest and that all copies of this mutation in the family are identical by descent.

www.jmedgenet.com
risks dropped by 20%, 31%, or 50% risk of 100% or 0%). The number of persons with carrier risk status (that is, the proportion of family members with carrier testing and disclosure of test results to family members, dra-
gereditary cancer syndrome family, followed by offering of

As expected, discovery of a specific pathogenic mutation in a

DISCUSSION
As expected, discovery of a specific pathogenic mutation in a

resulted from the testing and disclosure of a relative and were not
disclosed by us to the affected subject. Of the 2237 with
final carrier risk of 0, 825 or only 37% of the subjects had
disclosure by us. Of the 348 with a final carrier risk changed to
100%, 346 or 99% had disclosure by us. Of the 321 with
resulted from the testing and disclosure of a relative and were
identified and testing for the specific mutation has been made

The most common type of carrier risk change to result from
mutation testing was a change from at risk to non-carrier. This
accounted for 77% of the carrier risk changes in our cohort.
Before mutation testing, most of these people believed that
they were at some degree of increased risk, possibly leading to
anxiety, unnecessary cancer screening, and even prophylactic
surgery. After mutation testing, they could shed this burden,
but only if informed of their change in carrier risk status. The
next most common carrier risk change was a change to known
carrier; 12% of changes were of this type. Together, these types
of risk changes, which involve changing from uncertainty to
what is essentially certainty with respect to mutation carriage,
account for 89% of risk changes resulting from testing. The
remaining changes (11% of all cases with changed risk) had a
carrier risk increase from low risk to 25% or 50%, or from 25% to
50%, as a result of a positive mutation test in a close relative.
These results are applicable only to members of hereditary
cancer families where a specific pathogenic mutation has been
identified and testing for the specific mutation has been made
available. They do not apply to members of families where one
or more members have been examined for mutations but
where no mutations have been discovered, since in those cases
a negative result is much less informative, that is, it has a
much smaller effect on carrier risk. Our results also have lim-
ited application in families where a specific mutation has been
identified as a result of population based screening for muta-
tions, since in such cases no pre-testing carrier risks had been
assigned.

Changes in carrier risk can substantially affect cancer
prevention recommendations. If family members are follow-
ing these recommendations, there can be commensurate
changes in costs of medical care, risk resulting from screening tests and preventive procedures, and use of limited cancer control resources. Recommendations for screening do differ between known carriers and persons at 50% risk, so changes from 50% carrier risk to 100% are insignificant in this regard (although they may have important psychological and behavioural effects, including substantial effects on prophylactic surgery decisions). However, the 51 persons whose carrier risk changed from low or 25% to 100%, and the 281 persons whose carrier risk changed from low or 25% to 50%, would now be recommended to follow more intensive cancer screening regimens (see Table 3 for these and the following values). Of the 2237 persons identified as non-carriers after testing, 572 or 26% had been formerly classified as 50% carrier risk or higher. These persons would have been advised in the past to follow intensive cancer screening strategies associated with high risk; after testing they would be advised to follow the general population guidelines for cancer prevention.

The benefits associated with these changes in cancer preventive strategy, resulting from more accurate assessment of carrier risk, can only be achieved if family members are aware of their carrier risk status change. In our studies to date on HBOC and HNPCC, more than twice as many persons with carrier risk changes as a result of testing were actually tested and counselled. The size of the group with carrier risk changes but no counselling was unexpected, and raises troubling questions, discussed below.

It was expected that only a small proportion of family members would have been tested and counselled. During our family studies, family members at all levels of risk participated, but some members could not be contacted and others chose not to participate. When a mutation was discovered in a family member, we offered testing to high risk family members but not to those at low risk. We offered testing to the descendants of tested carriers if we knew that they had been informed of the carrier's test result, and we provided testing to high risk family members who requested it. Our offers of testing were sent by mail, as well as delivered verbally to family members who met us. Among high risk family members offered testing, approximately 40% chose not to be tested (HTL, unpublished data).

Reliance upon the tested and counselled person to inform relatives of his/her test result and its implications for their (the relative's) carrier risk is common medical practice. The alternative (the counsellor's disclosure of test information to the tested subject's relatives whose carrier risk status is affected by the test result) is constrained by the confidentiality of the tested subject's medical information.15-17 In counselling the tested person, our protocol includes discussing the effect of the test result on relatives' mutation carrier risk, and encouraging the tested person to inform those relatives of any changes. Of course, it is the tested subject's decision whom to inform. We do not know how often, or how effectively, the tested subjects communicated with family members whose carrier risk was affected by their test result. Smith et al.18 recently reported that test results are not consistently reported, especially by fathers, to descendants, especially sons. In our experience, some people who received a negative mutation test showed signs of disbelief in their new, negligible carrier risk; they continued to describe their own risk as high, they continued to have cancer screening which is not appropriate for a person at average risk, and they continued to worry about their children's risk of inheriting the mutation. These misperceptions cause concern about the misinformation which may be communicated to family members, especially the inferred non-carriers.

In conclusion, mutation testing increases the accuracy of carrier risk assessments, and produces a large decrease in the number of persons at high carrier risk. The most common risk assessment change to result from DNA testing was a change from at risk to non-carrier. To the extent that these persons were aware of their carrier risk and were obtaining heightened cancer surveillance testing, this can be expected to lead to a reduced emotional toll and reduced pressure on limited medical resources. Although we use a family oriented approach to education, risk assessment, and genetic testing,19 we noted that over half of the persons whose carrier risks were changed by mutation testing were not themselves tested and thus were not informed by us of the change in their risk status. We believe a study of the impact of testing on untreated, undisclosed family members is needed. Any study of this phenomenon will be complicated by the need to preserve the confidentiality of the medical information of the tested subjects. This situation is not substantially altered by the implementation of the Health Insurance Portability and Accountability Act (HIPAA), since we already required written authorisation to disclose individual study results to anyone other than the person studied. A way must be found to study the effect of testing on the relatives of the tested subject, without violating the subject's confidentiality, if we are to assess the full effect of genetic testing in hereditary cancer syndrome families. If it is found that the impact is truncated because intrafamily communication is inadequate, studies of barriers to communication and of interventions to improve communication within the family may be warranted.

ACKNOWLEDGEMENTS

This article was supported by revenue from Nebraska cigarette taxes awarded to Creighton University by the Nebraska Department of Health and Human Services. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the State of Nebraska or the Nebraska Department of Health and Human Services. Funding support was also provided through NIH Grant No. U01 CA86389-01.

Electronic database information. Accession numbers and URL for data in this article are as follows: Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/omim/ (for HNPCC (MIM 114500) and HBOC (MIM 113705; MIM 600185)).

Authors' affiliations

P Watson, J F Lynch, S T Tinley, C L Snyder, S A Coronel, B Riley, Y Kinarsky, H T Lynch, Department of Preventive Medicine and Public Health, Creighton University School of Medicine, Omaha, NE, USA

S A Narod, The Centre for Research in Women's Health, Toronto, Ontario, Canada

R Fodde, Department of Human Genetics, Leiden University, Leiden, The Netherlands

A Wagner, Department of Clinical Genetics, Erasmus University Medical Centre, Rotterdam, The Netherlands

REFERENCES


ECHO

A clinical, histopathological, and genetic study of Avellino corneal dystrophy in British families

M F El-Ashry, M M Abd El-Aziz, D F P Larkin, B Clarke, I A Cree, A J Hardcastle, S S Bhattacharya and N D Ebenezer

Aims: To establish a clinical, histopathological, and genetic diagnosis in two unrelated British families with Avellino corneal dystrophy (ACD).

Methods: Genomic DNA was extracted from peripheral blood leucocytes of all members participating in the study. Exons 4 and 12 of the human transforming growth factor β induced (BIGH3) gene were amplified by polymerase chain reaction. The mutation and polymorphism were identified by direct sequencing and restriction digest analysis. A review of the patients' clinical symptoms and signs was undertaken and a histopathological study on corneal specimen obtained from the proband of one family after keratoplasty was performed. Results: A heterozygous G to A transition at the second nucleotide position of codon 124 of BIGH3 gene was detected in all affected members of both families. This mutation changes an arginine residue to a histidine. The clinical diagnosis for ACD was more evident with advancing age. Histopathological study revealed granular deposits in the anterior stroma and occasional positive Congo red areas of amyloid deposition in the mid to deep stroma typical of ACD.

Conclusions: This is the first report of ACD families in the United Kingdom and, furthermore, of BIGH3 gene mutation in British patients with this rare type of corneal dystrophy. The results indicate that BIGH3 gene screening along with clinical and histopathological examinations is essential for the diagnosis and clinical management of corneal dystrophies.

▲ British Journal of Ophthalmology 2003; 87:839–842
Carrier risk status changes resulting from mutation testing in hereditary non-polyposis colorectal cancer and hereditary breast-ovarian cancer

P Watson, S A Narod, R Fodde, A Wagner, J F Lynch, S T Tinley, C L Snyder, S A Coronel, B Riley, Y Kinarsky and H T Lynch

doi: 10.1136/jmg.40.8.591

Updated information and services can be found at:
http://jmg.bmj.com/content/40/8/591

These include:

References
This article cites 17 articles, 5 of which you can access for free at:
http://jmg.bmj.com/content/40/8/591#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
- Colon cancer (131)
- Epidemiology (630)
- Prevention (5)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/