

ORIGINAL ARTICLE

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

J Med Genet 2003;**40**:591–596

See end of article for authors' affiliations

Correspondence to:
Dr P Watson, Department of Preventive Medicine and Public Health, Creighton University School of Medicine, 2500 California Plaza, Omaha, NE 68178, USA; patrice@creighton.edu

Revised version received 23 April 2003
Accepted for publication 24 April 2003

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 (HNPCC) 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, 1408 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 1408 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.

Cancer family history and personal medical history was, until recently, the only information available to determine a person's carrier risk for hereditary cancer syndromes, such as hereditary non-polyposis colorectal cancer (HNPCC, MIM 114500) or hereditary breast-ovarian cancer (HBOC, MIM 113705 and MIM 600185), which lack highly penetrant and specific signs like the florid polyposis seen in familial adenomatous polyposis.^{1,2} Cancer based assessment of the risk of carrying an HNPCC or HBOC mutation (that is, carrier risk assessment based on personal and family history of cancer, referred to as cancer based carrier risk) is inaccurate because of incomplete penetrance, inaccurate family history, phenocopies, and small family size. For example, in a hereditary cancer prone family, sporadic cancer (phenocopies) may occur among the relatives who do not carry the deleterious mutation, and this can produce misleading overestimates of carrier risk for the sporadic cases and their close relatives. On the other hand, since penetrance is incomplete, mutation carriers may be free of cancer, and this may also cause misclassification of family members' risk, leading to underestimates of the risk of mutation carriage. Even in this era of mutation testing,³ cancer based risk assessment may be the only option, either because family members refuse testing or because no mutation can be identified. Programs such as BRCA^{PRO}⁴ perform cancer based carrier risk assessment in a highly quantitative way.

More accurate individual carrier risk assessment is based on DNA testing.³ When a deleterious mutation has been found in one family member, subsequent DNA testing for this specific mutation in other family members can produce dramatic

changes in carrier risk. Before mutation testing, using cancer based carrier risk assessment, unaffected progeny of a cancer affected subject are all estimated to have a 50% risk of carrying the mutation. The carrier risk can be adjusted, based on age dependent penetrance models, but uncertainty is not dramatically reduced. With mutation testing, unaffected progeny of a tested mutation carrier can be tested and reclassified as either a carrier or a non-carrier. In this situation, the descendants of the non-carriers will also be reclassified as non-carriers, without being individually tested. Note that classification as a non-carrier (a carrier risk of zero) for a hereditary cancer syndrome family member is possible only when a clearly pathogenetic mutation has been shown to be segregating in the family.⁵ When carrier risk assessment is based solely on the personal and family history of cancer, none of the relatives of affected family members can be classified as "not at risk," even if only distantly related to family members with syndrome cancers. Furthermore, failure to find a mutation in a member of an HNPCC or HBOC family in which no mutation has yet been identified is uninformative and does not reduce carrier risk to zero.

Accurate carrier risk assessment is important because of its direct association with hereditary cancer risk. Decisions about cancer screening, cancer surgical management,^{6,7} and prophylactic surgery^{8–11} can be affected by knowledge of carrier risk. Underestimating carrier risk, and therefore cancer risk, may lead to reduced effort on cancer prevention and in turn to increased morbidity and mortality. Conversely, as a consequence of overestimation of carrier risk and, thereby, cancer risk, subjects may experience unnecessary lifelong anxiety^{12–14},

Table 1 Definitions for inclusion rules and carrier risk classification rules

Progenitor, HNPCC family	The closest common ancestors of all mutation carriers by test, plus cases with any of the following: endometrial cancer age <50, colon cancer age <50, multiple colon/endometrial cancer
Progenitor, HBOC family	The closest common ancestors of all mutation carriers by test plus cases with any of the following: breast cancer age <50, ovarian cancer any age, or multiple breast/ovary cancer
HNPCC cancer	Invasive cancer of the colon, endometrium, ovary, stomach, or small bowel, or an invasive transitional cell carcinoma of the kidney or ureter
HBOC cancer	Invasive cancer of the breast or ovary
Known carrier	A direct test for a specific mutation, previously identified in other family members, was positive and results were disclosed
Known non-carrier	A direct test for a specific mutation, previously identified in other family members, was negative and results were disclosed

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 phenocopy 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 HNPCC¹ and HBOC² 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 259 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 2 Carrier risk classification among the descendants of progenitors.

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

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.

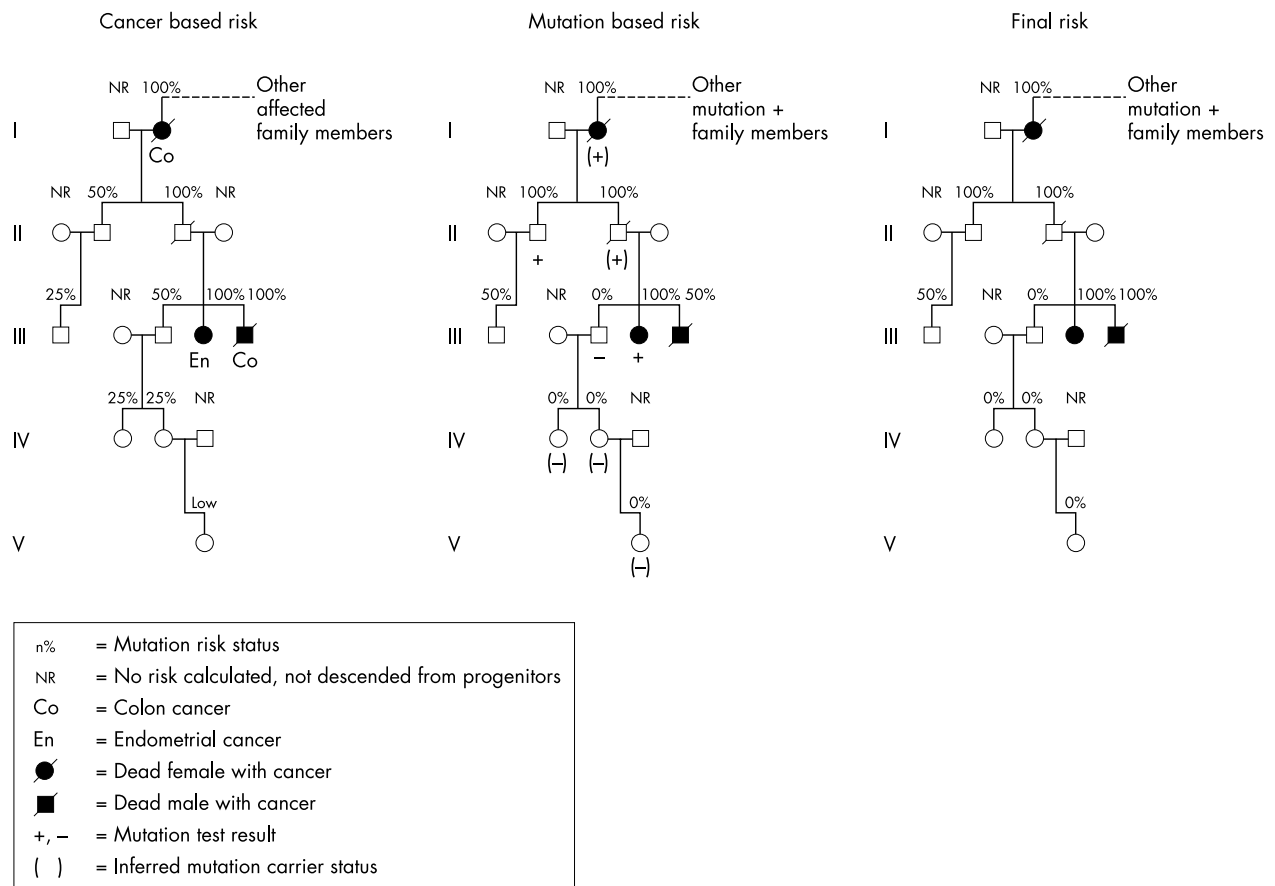


Figure 1 An illustration of the application of rules for assigning carrier risk based on cancer family history and mutation test results in an HNPCC family. Note that in all these cases except one (colon cancer case in generation III), since mutation test based carrier risk is either zero, equal to, 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.

100%. 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).

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.

Cancer based carrier risk	Final carrier risk					Total
	0%	Low	25%	50%	100%	
Low	771	3420	40	29	4	4264
25%	894	0	2535	252	47	3728
50%	550	0	0	1608	297	2455
100%	22	0	0	0	441	463
Total	2237	3420	2575	1889	789	10 910

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.

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).

Routinely in our genetic testing and counselling procedures, we provide genetic counselling covering test results and carrier risk status changes to the tested subjects. In this cohort there were 1408 subjects to whom we disclosed mutation test results. This number includes the 237 tests which resulted in no change in carrier risk status. These tests, since they did not change the carrier risk status of the tested subject, did not affect the carrier risk of that person's relatives. The other 1171 tests resulted in a change in carrier risk status. These 1171 tests resulted in changes in carrier risk status for 2906 persons, the 1171 tested subjects and 1735 of their untested relatives. Hence, only 40% of the persons with a carrier risk status change had that change as a result of their own mutation test; only that 40% had their carrier risk status change disclosed by us. The majority, 60%, of carrier risk changes

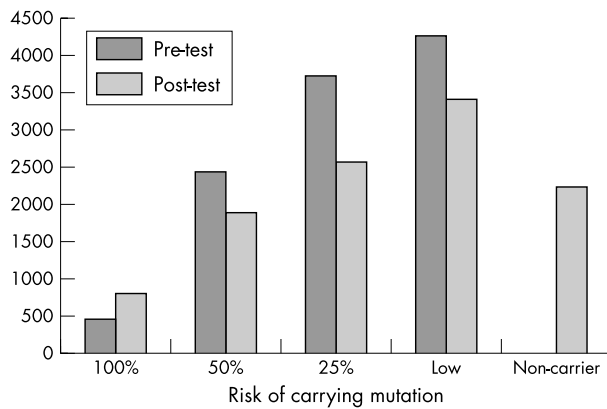


Figure 2 Carrier risk distribution among 10910 HBOC and HNPCC family members before and after mutation testing and results disclosure to 1408 members of these families.

Table 4 Number of cases in each final carrier risk class, broken down by original (cancer based) carrier risk class, including only HNPCC family members whose carrier risk class changed as a result of mutation testing of 678 family members

Cancer based carrier risk	Final carrier risk				Total
	0%	25%	50%	100%	
Low	461	15	9	0	485
25%	432	0	92	18	542
50%	274	0	0	150	424
100%	12	0	0	0	12
Total	1179	15	101	168	1463

Table 5 Number of cases in each final carrier risk class, broken down by original (cancer based) carrier risk class, including only HBOC family members whose carrier risk class changed as a result of mutation testing of 730 family members

Cancer based carrier risk	Final carrier risk				Total
	0%	25%	50%	100%	
Low	310	25	20	4	359
25%	462	0	160	29	651
50%	276	0	0	147	423
100%	10	0	0	0	10
Total	1058	25	180	180	1443

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 changes to intermediate levels of carrier risk, none had disclosure by us.

DISCUSSION

As expected, discovery of a specific pathogenic mutation in a hereditary cancer syndrome family, followed by offering of testing and disclosure of test results to family members, dramatically increased the extent of certainty about carrier risk status (that is, the proportion of family members with carrier risk of 100% or 0%). The number of persons with carrier risk classification of low, 25%, or 50% risk dropped by 20%, 31%,

and 23%, respectively, relative to their pre-testing frequency, while the number classified as carriers (carrier risk 100%) increased by 70%. The category of non-carrier (by test or inference), which did not exist before testing, included 20% of all family members after testing.

It was expected that the carrier risk distribution would shift towards lower risk after testing, but the size of the shift was surprising. The preponderance of carrier risk decreases was mainly because a negative mutation test affects more family members than does a positive test, since all descendants of a person who tests negative are reclassified as non-carriers. In our cohort, each negative test was associated with carrier risk decrease for an average of 2.7 people, while each positive test was associated with a carrier risk increase for an average of 1.1 person. Another factor contributing to the shift towards lower risk was the excess of negative tests over positive mutation tests. Only 583 or 41% of 1408 mutation tests were positive. Since testing for an identified pathogenic mutation is extremely sensitive and specific, the proportion of positive tests is a function of the pre-test carrier risk distribution of the tested family members. If another genetic testing service used different methods that caused a higher proportion of positive tests (for example, including only first degree relatives of index cases with a known mutation), they would have a smaller shift in the carrier risk distribution as a result of testing; however, because negative tests produce more risk decreases than positive tests produce risk increases, the shift would still be in the direction of lower carrier risk.

It will be noted that the number of positive tests in our cohort was less than expected from the distribution of cancer based carrier risks. Our method of assigning cancer based pre-test carrier risk (table 2) was expected to overestimate the true carrier risk, since it is not adjusted for the age of the person. For example, two unaffected first degree relatives of a cancer affected family member are both assigned the same cancer based carrier risk of 50%, even if one is 20 years of age and the other is 60 and thus considerably less likely than the 20 year old to be a mutation carrier. (Age adjusted risks were not used in our analysis because they are not used in our clinical practice; they are not associated with differences in management recommendations.)

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 limited application in families where a specific mutation has been identified as a result of population based screening for mutations, 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 following 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 not 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 had carrier risk changes as a result of testing as 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 subjects' 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 untested, 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 1U01 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

- 1 **Lynch HT,** de la Chapelle A. Genetic susceptibility to non-polyposis colorectal cancer. *J Med Genet* 1999;**36**:801-18.
- 2 **Lynch HT,** Snyder CL, Lynch JF, Riley BD, Rubinstein WS. Hereditary breast-ovarian cancer at the bedside: role of the medical oncologist. *J Clin Oncol* 2003;**21**:740-53.
- 3 **Vogelstein B,** Kinzler KW, eds. *The genetic basis of human cancer.* New York: McGraw-Hill, 1998.
- 4 **Berry DA,** Iversen ES Jr, Gudbjartsson DF, Hiller EH, Garber JE, Peshkin BN, Lerman C, Watson P, Lynch HT, Hilsenbeck SG, Rubinstein WS, Hughes KS, Parmigiani G. BRCA1/BRCA2 validation, sensitivity of genetic testing of BRCA1/BRCA2 and prevalence of other breast cancer susceptibility genes. *J Clin Oncol* 2002;**20**:2701-12.
- 5 **Lynch HT,** Watson P, Tinley S, Snyder C, Durham C, Lynch J, Kinarsky Y, Serova O, Lenoir G, Lerman C, Narod SA. An update on DNA-based BRCA1/BRCA2 genetic counseling in hereditary breast cancer. *Cancer Genet Cytogenet* 1999;**109**:91-8.
- 6 **Burke W,** Petersen G, Lynch P, Botkin J, Daly M, Garber J, Ellis Kahn MJ, McTiernan A, Offit K, Thomson E, Varricchio C, for the Cancer Genetics Studies Consortium. Recommendations for follow-up care of individuals with an inherited predisposition to cancer: I. Hereditary nonpolyposis colon cancer. *JAMA* 1997;**277**:915-19.
- 7 **Burke W,** Daly M, Garber J, Botkin J, Ellis Kahn MJ, Lynch P, McTiernan A, Offit K, Perlman J, Petersen G, Thomson E, Varricchio C, for the Cancer Genetics Studies Consortium. Recommendations for follow-up

- care of individuals with an inherited predisposition to cancer. II. *BRCA1* and *BRCA2*. *JAMA* 1997;**277**:997-1003.
- 8 **Lynch HT**. Is there a role for prophylactic subtotal colectomy among hereditary nonpolyposis colorectal cancer germline mutation carriers? *Dis Colon Rectum* 1996;**39**:109-10.
 - 9 **Hartmann LC**, Sellers TA, Schaid DJ, Frank TS, Soderberg CL, Sitta DL, Frost MH, Grant CS, Donohue JH, Woods JE, McDonnell SK, Walsh Vockley C, Deffenbaugh A, Couch FJ, Jenkins RB. Efficacy of bilateral prophylactic mastectomy in *BRCA1* and *BRCA2* gene mutation carriers. *J Natl Cancer Inst* 2001;**93**:1633-7.
 - 10 **Lynch HT**, Lynch JF, Rubinstein WS. Prophylactic mastectomy: obstacles and benefits. *J Natl Cancer Inst* 2001;**93**:1586-7.
 - 11 **Rebbeck TR**, Lynch HT, Neuhausen SL, Narod SA, van't Veer L, Garber JE, Evans G, Isaacs C, Daly MB, Matloff E, Olopade OI, Weber BL, for The Prevention and Observation of Surgical End Points Study Group. Prophylactic oophorectomy in carriers of *BRCA1* or *BRCA2* mutations. *N Engl J Med* 2002;**346**:1616-22.
 - 12 **Lynch HT**, Watson P, Shaw TG, Lynch JF, Harty AE, Franklin BA, Kapler CR, Tinley ST, Liu B. Clinical impact of molecular genetic diagnosis, genetic counseling, and management of hereditary cancer. Part I: studies of cancer in families. *Cancer* 1999;**86**:2449-56.
 - 13 **Lynch HT**, Watson P, Shaw TG, Lynch JF, Harty AE, Franklin BA, Kapler CR, Tinley ST, Liu B, Lerman C. Clinical impact of molecular genetic diagnosis, genetic counseling, and management of hereditary cancer. Part II. Hereditary nonpolyposis colorectal carcinoma as a model. *Cancer* 1999;**86**:2457-63.
 - 14 **Aktan-Collan K**, Haukkala A, Mecklin J-P, Uutela A, Kääriäinen H. Psychological consequences of predictive genetic testing for hereditary non-polyposis colorectal cancer (HNPCC): a prospective follow-up study. *Int J Cancer* 2001;**93**:608-11.
 - 15 **Benkendorf JL**, Reutenauer JE, Hughes CA, Eads N, Willison J, Powers M, Lerman C. Patients' attitudes about autonomy and confidentiality in genetic testing for breast-ovarian cancer susceptibility. *Am J Med Genet* 1997;**73**:296-303.
 - 16 **Julian-Reynier C**, Eisinger F, Chabal F, Lasset C, Noguès C, Stoppa-Lyonnet D, Vennin P, Sobol H. Disclosure to the family of breast/ovarian cancer genetic test results: patient's willingness and associated factors. *Am J Med Genet* 2000;**94**:13-18.
 - 17 **Veatch RM**. Consent, confidentiality, and research. *N Engl J Med* 1997;**336**:869-70.
 - 18 **Smith KR**, Zick CD, Mayer RN, Botkin JR. Voluntary disclosure of *BRCA1* mutation test results. *Genet Test* 2002;**6**:89-92.
 - 19 **Lynch HT**. Family Information Service and hereditary cancer. *Cancer* 2001;**91**:625-8.

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



Please visit the Journal of Medical Genetics website [www.jmedgenet.com] for a link to this full article.

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