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PRECLINICAL STUDY

Direct-to-patient BRCA1 testing: the *Twoj Styl* experience

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Abstract Ideally, a genetic screening program for cancer should offer testing to all women who qualify, and who wish to participate, and who might benefit from the test. As the number of preventive options for women at high risk for hereditary breast cancer expands, the demand for testing increases. However, many women do not have ready access to testing because of cost, and many others have not been recognized by their physicians to be candidates for testing. It is possible to increase women's awareness about hereditary cancer through the popular press. Genetic testing was offered to 5000 Polish women through an announcement placed in a popular women's magazine (*Twoj Styl*) in October 2001. A total of 5024 women who qualified received a free genetic test for three mutations in BRCA1 which are common in Poland. Out of these, 198 women (3.9%) were found to carry a BRCA1 mutation. The overall cost per mutation detected was 630 US dollars—approximately 50–100 times less than the equivalent cost in North America. Genetic counseling was offered to women with a positive test or with a significant family history of breast or ovarian cancer. The great majority of women who took part in the program expressed a high degree of satisfaction and after one year approximately two-thirds of identified mutation carriers had complied with our recommendations for breast cancer screening. We found this model of genetic testing and delivery of genetic information to be very efficient in a population in which founder mutations predominate. There is a need for similar studies in other populations.

Keywords BRCA1 · Genetic counseling · Breast cancer · Ovarian cancer

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Introduction

We explore the consequences of allowing women to be the gatekeepers of their access to testing for genetic susceptibility to hereditary breast cancer. Under this paradigm, women are provided with basic printed information about genetic testing and are invited to apply for genetic testing on their own behalf. Comprehensive counseling is offered to women with a mutation or with a strong family history. This contrasts with the usual care model whereby the patient is referred for genetic testing by a physician and each woman receives intensive counseling before and after disclosure. In our alternate scenario the onus is placed on the woman to be aware of her family history of cancer and to judge when it is appropriate for her to seek further information about risk evaluation and risk reduction. We believe that under this model benefits will accrue to individuals and on a population level. Patients may benefit because genetic testing becomes more widely available and access to testing is not

restricted by local medical practitioners, who may vary in their levels of knowledge and their attitudes. In the population at large it is possible to maximize the number of mutation carriers identified at a given cost.

It is challenging to identify all women in a population who carry a BRCA1 mutation. This problem will be compounded when more effective means of preventing cancer in predisposed women are discovered, and demand for genetic testing increases. Currently, in most clinics, women who are to undergo genetic testing receive at least one personal (one-on-one) counseling session (or a series of sessions) where they receive detailed information regarding what to expect in the event of a positive test. Because personalized counseling is expensive and time-consuming, testing is usually restricted to women who have a high chance of carrying a mutation and who have adequate resources at their disposal (through private or public means). We propose that a reasonable alternative is to focus counseling efforts on women who receive a positive test or who have a positive family history. Women who are not at increased risk (i.e. who have a negative test and no strong family history) probably do not require detailed personalized information and will not be compromised by streamlining of the genetic testing process. Research on psychosocial functioning has shown reduced levels of distress among women who receive a negative BRCA1 or BRCA2 mutation result [1, 2]. Therefore, we do not expect that women with a negative genetic result require personalized follow-up. Our resources can then be focused on increasing the number of genetics tests performed and on counseling those who have a positive result or a strong family history, and who are therefore candidates for special interventions.

The frequency of mutations and the cost of mutation testing vary dramatically between populations and no single scenario applies to all countries. The cost and yield of a genetic test are strongly influenced by whether or not a local founder effect is present and whether testing can be restricted to a small number of common mutations. Mutations may occur in women with little or no family history of cancer, and who may not qualify for testing under conventional criteria. As a result many (if not most) mutations in a population would be missed if testing were restricted to those with a high prior probability of a positive result. As testing criteria are loosened, more mutations will be found—but there will be a significant increase in the amount of resources required to find these additional mutations and to counsel those tested—unless more resource-efficient counseling strategies are implemented.

Ultimately the success of a genetic testing program will come from saving the lives of some of the women who participate in the program. Prior to endorsing the model of offering genetic services directly to large numbers of women at modestly elevated risk it is prudent that we evaluate the consequences of such a program. Issues to consider include the number of women who wish to participate, the cost per mutation detected, the satisfaction of women who participate in the program, and the access to and utilization of preventive services among women in the program. Groups of women who test positive and who test negative should be evaluated separately, and both groups should benefit from the process.

Testing protocol

In October 2001 a popular Polish women's magazine (*Twoj Styl* or *Your Style*) published a supplement dealing with breast cancer. This is among the best known women's magazines in Poland and has a circulation of 400,000. The issue contained an article dealing with issues surrounding hereditary breast cancer, including the state of genetic testing in Poland and the possible risks and benefits of genetic testing. Various ways of reducing cancer risk were described. In collaboration with the Hereditary Cancer Center at the Pomeranian Medical University, the publishers of *Twoj Styl* offered an opportunity for 5000 of their readers to participate in genetic testing at no cost. Women qualified if they were 18 years of age or over and if they had a first- or second-degree relative with breast cancer before age 50 or ovarian cancer at any age, or if they themselves had such history of breast or ovarian cancer. Readers who qualified could clip a coupon inviting them for genetic testing and present the coupon at one of 20 familial cancer outpatient clinics situated throughout the country. Approximately 10,000 women applied for testing. *Twoj Styl* agreed to pay 100 zloty per patient (roughly 25 US dollars) to cover the costs.

When the woman arrived at the clinic she presented her coupon and her indications for testing were confirmed by the local staff. If she qualified she signed a consent form and she gave a blood sample for testing. A brief intake form was completed regarding family history and personal history of cancer. Genetic testing was done for the three founder BRCA1 mutations, which are common in the Polish population. A total of 5024 tests were completed between November 2001 and February 2002 at the Hereditary Cancer Center in Szczecin.

In the event of a positive test the patient was invited by letter to attend a personal counseling session at the center where she gave blood. If she did not come forward within two months she was prompted by a telephone call to come to the clinic to receive her result. If the genetic test was negative and the family history was positive (two or more cases of breast or ovarian cancer or one breast cancer case diagnosed at age less than 40) the patient was also invited for personalized genetic counseling. In the event of a negative test and no family history, the patient was invited to receive her result at the center, but without a counseling session. In these cases, the recommendations for surveillance were those for the general population. Non-carriers who were reluctant to receive their result in person were offered to receive their result by letter or by telephone. Women who wished to have personalized counseling were offered counseling regardless of their test result or family history.

The post-test counseling sessions were designed to address the woman's specific risk situation—based on her genetic test result, her age, her cancer status and her family history. A list of recommendations was printed for each of six different risk scenarios (available upon request). The session took approximately 45 min and the patient was referred to an oncologist or surgeon when appropriate. Specific recommendations to unaffected women with a strong family history included a clinical breast examination every 6 months, annual mammography from age 35 and ovarian ultrasound from age 35. Mutation carriers were advised in addition to undergo a bilateral prophylactic oophorectomy by age 40. Prophylactic bilateral mastectomy was discussed as an option for breast cancer prevention but was not routinely recommended. If the patient had a mutation and a previous history of breast cancer an oophorectomy was recommended and contralateral mastectomy and tamoxifen were discussed. Cancer patients were advised to discuss these recommendations with their medical oncologists.

Study protocol

A questionnaire was sent to a sample of the study subjects approximately 1 year after they received the test result. The questionnaire dealt with the knowledge of the test results and the satisfaction with the testing process (available upon request). Women were asked whether or not they valued the testing process and whether they were satisfied with their decision to participate. Women were questioned about cancer prevention practices over the past year. Questionnaires were sent to all 198 women with a positive genetic result and to a random sample of 280 women without mutations.

Results

Among the 5024 women who received testing 198 BRCA1 mutations were identified (3.9%). A questionnaire was received from 126 women with a positive genetic test result (72%). Six carrier women had died and two refused. Twenty-six women were lost to follow-up and 15 did not respond. Of the 126 carriers who responded, 63 women had a past history of cancer and 63 had no history of cancer. A random sample of 280 non-carriers was selected. Of these 173 (62%) returned the questionnaire. Twenty-eight of these (16%) had a past history of breast or ovarian cancer and 145 had no history of cancer. Two questionnaires from non-carriers were returned but contained insufficient information to include them in the analysis. Because we are primarily interested in the experience of genetic testing in women without cancer the following analysis are restricted to 63 carriers and 143 non-carriers with no personal history of breast or ovarian cancer. The average age of the 143 non-carriers was 44 years (range 27–74 years). About 30% of the non-carriers had a significant family history of cancer (two or more affected relatives or a single relative diagnosed with breast cancer under age 40) and 70% had only a single affected relative (and no relative diagnosed under age 40). The non-carrier women with a strong family history of cancer and also received personalized counseling.

The mean age of the BRCA1 carriers was 45.6 years (range 27–73) and of the non-carriers was 44.1 years (range 27–74). About 59% of the BRCA1 carriers had an education level greater than high school, compared to 69% of non-carriers. The majority of carriers and non-carriers were married or in a common-law relationship (81.7% and 89.5%, respectively).

Fifty-four of the 63 carriers (86%) went to the testing center to receive their result after being informed by letter that her result was ready. An additional eight carriers did not respond to the letter but were prompted by a telephone call to return to the center to receive their result (one carrier did not answer the question). Upon receiving the positive test result the most common immediate reactions among mutation carriers were worry (36.5%), shock (27%) and sadness (22%). Among non-carriers the most common reactions were relief (63.5%) and happiness (29.5%).

A total of 81% of the carriers felt that they had been adequately informed about preventive measures during the counseling session, but 19% wished to have more information. Carriers recall having discussed during the counseling session the importance of prophylactic oophorectomy (65% of respondents), mammography (62%), breast self-examination (47.5%), ovarian ultrasound (43%), clinical breast examination (36.5%), prophylactic mastectomy (33%) and screening with CA-125 (30%). Non-carriers at high familial risk recalled discussing mammography (63%), clinical breast examination, (46.5%) and breast self-examination (65%). Less frequently did this group recall discussing screening measures for ovarian cancer (24% for ovarian ultrasound and 6.5% for CA-125). Prophylactic oophorectomy was discussed only rarely (5%). On average, carriers estimated their lifetime risk of breast cancer to be 60.5% and of ovarian cancer to be 48%. Non-carriers with a strong family history estimated their lifetime risk for breast cancer to be 29% on average and estimated their lifetime risk of ovarian cancer to be 22%. Non-familial non-carriers estimated their breast cancer risk, on average to be 13% and their ovarian cancer risk to be 8.5%. Only 18% of the women in this group estimated their breast cancer risk to be less than 10%. On average, carriers utilized preventive measures more frequently than non-carriers (Table 1). Approximately two-thirds of the carriers and just over one-half of the familial non-carriers had complied with the annual recommendations for breast cancer screening. Compliance was much less for ovarian cancer prevention. Satisfaction rates among the subjects were very high. 98% of the women indicated that they would recommend genetic testing to other women in their position. The proportion of satisfied women was equally high among carriers (98%) and non-carriers (97%).

Discussion

By placing a single announcement in a popular women's magazine we were able to identify 198 carriers of BRCA1 mutations who otherwise might not have been identified through the regular health care system. The magazine agreed to support the costs of testing for only one-half of the women who applied to this program, otherwise the final yield of this announcement might have been closer to 400 carriers. Based on this experience we anticipate that 100,000 or more women would be encouraged to apply for testing if a similar announcement were to be placed on a few occasions in several magazines. This appears to us to be an attractive way of initiating interest in genetic testing.

The total cost of the program was about 125,000 US dollars, or roughly 631 dollars per mutation carrier detected. This compares with an outlay of approximately 30,000 dollars per mutation detected in North America (assuming 3,000 dollars per test and a positivity rate of 10%) exclusive of the costs of genetic counseling (the cost of counseling in the US is often between 250–300 dollars per patient). The enormous difference in efficiency is the result of several factors: (1) laboratory costs in Poland are much lower because it is necessary to look for only three founder mutations, rather than scan the entire gene; (2) BRCA mutations are more common in breast cancer families in Poland than in North America; (3) labor costs are cheaper in

Table 1 Proportion of women in study who had preventive measures

	Carriers (n = 63)	Non-carriers	
		Family history + (n = 43)	Family history– (n = 99)
A. Breast cancer			
Mammography in past year[a]	71%	62%	54%
BSE (mean per year)	13.4	11.6	7.5
CBE in past year	68%	58%	50%
Prophylactic mastectomy	5%	0%	0%
B. Ovarian cancer			
Ovarian ultrasound	67%	60%	39%
CA-125	56%	21%	9%
Prophylactic Oophorectomy[b]	23%	2%	4%

[a]Restricted to women age 35 or over

[b]Restricted to women age 40 or over

BSE: breast self-examination

CBE: clinical breast-examination

Poland than in North America and; (4) the genetic counseling process was streamlined and (5) when genetic testing is offered for free the costs associated with marketing are negligible. In North America, it is possible to test for three founder mutations among Ashkenazi Jews for approximately 300 dollars, or 3000 dollars per mutation detected, exclusive of genetic counseling.

In particular, we believe that were able to implement this program because we adopted a non-traditional model of genetic counseling. Pre-test counseling visits were short and blood samples were taken at the first appointment. Women with a negative family history and a negative BRCA1 test did not receive genetic counseling when they received their result unless requested. Based on our study sample we estimate that 1760 of the 5000 women had either a positive genetic test or a strong family history and were candidates for full counseling sessions. This represents 35% of the sample who underwent genetic testing.

Considerable savings were realized through abbreviating the pre-test counseling process and eliminating post-test counseling for most women with a negative test. But are there possible harms incurred by this? The potential harms of testing people without extensive counseling have been well described, but remain largely theoretical 10 years after genetic counseling for breast cancer was introduced. Concerns have been raised that women might develop a false sense of security if they were to over-interpret a negative test. However, in our sample the average women with a negative test estimated her risk of breast cancer to be 19%, and only 18% considered their risk to be less than 10%. No woman estimated her risk to be zero. Previous research has reported that women often over-estimate their breast cancer risk both in the genetics clinic and in the general population [3–7]. Even after genetic counseling, women have been shown to continue to over-estimate their risk of breast cancer by 23–25% [3, 4].

The majority (57%) of these women had a mammogram during the previous year and, on average, performed nine breast self-examinations annually. Compliance was less for ovarian cancer screening. It is not surprising, however, that few women had a CA-125 test in the past year given that only 30% of the women recall this being a topic of discussion during the counseling session. In North America we found that 55% of the mutation carriers were screened regularly with CA-125 [8]. About 23% of the carriers over age 40 had undergone prophylactic oophorectomy but we expect that many more of these women will have this operation shortly. In a previous study we reported that 60% of BRCA1 carriers counseled at a single center in Szczecin had undergone a prophylactic oophorectomy within 19 months of receiving their result [9].

It also is possible that there were false negative test results. We previously reported that the three founder mutations represent 86% of all BRCA mutations in Poland [10]. It is expected therefore that we have missed about 30 (non-founder) mutations in the 5000 women, but it is not clear what the negative consequence of this could have been, given that these women had not been offered genetic evaluation elsewhere and testing for other mutations is not now in place. These potential harms must be weighed against the benefits of identifying 198 women with pathogenic mutations.

And what are the possible harms of a positive genetic test? Concerns have been raised over the past decade about increasing psychological distress and possible insurance discrimination. As expected most of the women initially expressed shock or worry, but 98% of the carriers said that they would recommend the test to others. We observed similar levels of satisfaction in North America when standard comprehensive genetic counseling was offered [8, 11, 12], suggesting that the mode of delivery of counseling is unlikely to have a great impact on satisfaction levels. We did not measure psychological distress in this study, but there is no reason to believe that many women were unhappy with testing given that they almost universally endorsed the procedure. However, 15 women did not respond to our request and that these women may have experienced more psychological distress than the women who did respond. Previous studies have found that long-term psychological distress is rare following the receipt of a positive genetic test result [13]. In our experience, neither job discrimination nor insurance discrimination has been issues in Poland in relation to BRCA testing.

Nevertheless, we believe that a small proportion of women will not benefit from genetic testing, or should defer genetic testing. We do not recommend genetic testing to women below the age of 18. We do not encourage the testing of pregnant women and we ask that they defer the test until six months after childbirth. Some women worry excessively about cancer and are psychologically vulnerable. Their distress may be exacerbated by a positive test (but worry may also be alleviated by preventive mastectomy [14]).

One might argue that using more stringent testing criteria would reduce the number of tests performed, and thereby reduce program costs. About 40% of the carriers identified in this study had little, or no, family history. Among these women, the prevalence of mutations was approximately 2%—or 1250 dollars per mutation identified. We believe, therefore, that the

investment of testing low-risk women to be warranted. In a recent companion study, we performed genetic testing on 3500 unselected breast cancer patients diagnosed at or below 50 years of age [15]. Over 40% of the BRCA1 carriers had negative family history [15]. We believe that the results of this cost analysis support the wider use of testing in populations with common founder mutations, and may be generalized to the Jewish, French-Canadian and Icelandic populations. The model is currently being evaluated in several Latin American countries.

Ours study was conducted in a non-profit setting, but direct-to-consumer marketing of genetic testing has also been evaluated in North America. Mouchawar and colleagues evaluated a program of direct-to-consumer testing introduced by Myriad genetics to patients insured by Kaiser-Permanente in Colorado [16]. They observed a 244% increase in the demand for genetic testing. Increased interest in testing was observed in both the low-risk and high-risk groups of women.

Access to genetic testing in Poland is now widespread. All women with a first- or second-degree relative with breast cancer diagnosed at or before age 50, or with ovarian cancer diagnosed at any age, qualify for testing for the three common BRCA1 founder mutations, at no cost. The costs are born by National Health Service programs, through the National Foundation of Health and the Polish Ministry of Health. There are currently 22 hereditary cancer clinics in operation in Poland. However, the extent to which eligible women are aware of the availability of testing, and the proportion of women who live in proximity to one of these clinics, are unknown. We believe that communication with oncologists, geneticists and general practitioners is important to improve patient awareness, but we also believe that delivery of information about hereditary cancer and genetic testing by media is also beneficial.

It is our impression that there is little empiric evidence to support the near-universal recommendation that comprehensive genetic counseling be a prerequisite to genetic testing. The recommendation is largely historical and anecdotal and may be more a reflection of the interests of the health care providers than of the health care consumers. We encourage others to consider the public health consequences of policies surrounding the provision of genetic services in their communities, especially when resources are limited and services are not available to all. One of the goals of any screening program is that screening should be generally available to all individuals who are eligible, who wish to participate and who might benefit. We identified a very large number of carriers who otherwise would not have been aware of their mutation status—these women believe that they have gained by this knowledge and satisfaction with the program was almost universal. We found this model of genetic testing and delivering of genetic information to be effective in Poland and we hope that similar evaluations will be conducted in other countries.

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