Genetic counseling for patients and families with hereditary breast and ovarian cancer in a developing Asian country: an observational descriptive study

Sook-Yee Yoon · Meow-Keong Thong · Nur Aishah Mohd Taib · Cheng-Har Yip · Soo-Hwang Teo

Abstract Genetic counseling (GC) and genetic testing are vital risk management strategies in hereditary breast and ovarian cancer (HBOC) syndromes. Hitherto, cancer genetic testing amongst Asians has been described only in developed and high-income Asian countries. We studied the uptake and acceptance of GC and genetic testing services to Asian BRCA carriers in a middle-income country. A total of 363 patients were tested by full sequencing and large rearrangement analysis of both BRCA1 and BRCA2 genes in the Malaysian Breast Cancer (MyBrCa) Genetic Study. Of these, 49 index patients (13.5%) were found to carry deleterious mutations. GC pre- and post-result disclosures were provided and these groups of patients and their families were studied. GC and genetic testing were accepted by 82% of Malaysian patients at high risk for HBOC syndromes. However, risk assessment was limited by large, geographically dispersed, often polygamous or polyandrous families, and the lack of complete cancer registry. Cultural taboos about cancer diagnoses, social marginalization and lack of regulatory control of genetic discrimination were significant concerns. Only 78% of index patients informed their families of their risks and 11% of relatives came forward when offered free counseling and testing. Even when GC and genetic testing are provided at no cost, there remain significant societal and regulatory barriers to effective cancer genetic services in this underserved Asian population. Families believe there is a need for regulatory protection against genetic discrimination. Further studies are needed in the area of increasing awareness about the potential benefits of GC and genetic testing in Asians.

Keywords Genetic counseling · Cancer genetics service · Asian population · Hereditary breast and ovarian syndrome · Genetic discrimination

Introduction

World-wide, cancers are an increasingly important chronic disease [1]. Disparities in cancer care have emerged as an increasing concern in developing countries, including the provision and uptake of cancer genetic services [2, 3]. Provision of such services in developing countries [4] and uptake of such services in minority communities in developed countries [3, 5] are constrained by the limited knowledge about genetic mutations in different ethnic groups, the limited studies on uptake of clinical genetics services and the lack of funding and resources for these services.

Our understanding about attitudes towards genetic testing for predisposition genes for cancers in non-Caucasian
populations are largely based on studies done on minority populations, particularly amongst the African-American and Hispanic populations in the United States [3, 6–10]. In these populations, disparities in uptake of cancer genetic services have been described and may be attributable to differences in exposure to genetic information and referral by health care providers, but are not explained by differences in risk factors for carrying a BRCA1/2 mutation, socioeconomic factors, risk perception, or attitudes. The disparities persist even when barriers of ascertainment and cost were minimized [6, 10].

To date, cancer genetic testing amongst Asians has been described only in developed and high-income Asian countries [5, 11]. There have been few reports on the acceptance of genetic counseling in other Asian settings, particularly in low- and middle-income countries [12], in part because in these settings, genetic testing has hitherto been conducted in research settings, where the results of the genetic test are often undisclosed to research [13–18].

Genetic testing involves complex medical and psychological issues and has important ethical, social and legal implications for the individuals and their families. The acceptance of genetic testing and genetic counseling and its psychosocial impact are modulated by religious, cultural, social, educational and other factors [21–23], but studies of the role of these factors in the client interaction in cancer genetic counseling in Asians in developing countries have not been reported. In addition, with limited resources and genetic expertise in developing countries, it is crucial to determine the feasibility of establishing a cancer genetic counseling service to enable better planning and allocation of scarce healthcare resources.

Malaysia is a typical Asian developing country with a diverse population of 25 million, consisting of the three main Asian ethnic groups: the Malays and Indigenous groups (65%), Chinese (26%) and Indians (8%) [19]. Breast cancer is the most common cancer among women, although incidence differs between the ethnic groups [1 in 16 Chinese, 1 in 17 Indians and 1 in 28 Malays] and the age standardized incidence rate is lower than that in developed populations [20]. This paper reports the outcome of cancer genetic counseling in a diverse cohort of patients participating in a breast cancer genetic study.

Methods

Between January 2003 and December 2009, a total of 1,094 breast cancer patients were recruited for a study regarding genetic risk factors for breast cancer in Asian women (MyBrCa: Malaysian Breast Cancer Genetic Study). Patients were interviewed regarding their family history of any cancer. Patients were tested for BRCA1 and BRCA2 if they were considered high-risk. In addition, approximately 50% of patients who were considered of medium risk were included for analysis. Details of these studies were reported elsewhere [13, 14]. Based on these criteria, 363 patients were comprehensively tested by full sequencing and large rearrangement analysis of both BRCA1 and BRCA2 genes. Of these, 49 index patients (13.5%) were found to carry deleterious mutations [15].

When the study was initiated in 2003, the University Malaya ethics committee decided that patients should not be notified of their results, because the BRCA1 and BRCA2 mutation profiling were conducted in a research (not diagnostic) laboratory in Malaysia. The ethics committee determined that it was unclear of the benefits in informing the patients about the results. In 2007, with the identification of women bearing deleterious mutations and independent verification of laboratory results, the ethics approval was amended to enable patients with deleterious to be contacted for genetic counseling.

Since August 2007, all 49 women with deleterious mutations were approached to determine whether they wanted to know the results of the genetic test. Four patients have since died or were lost to follow-up and were therefore excluded from this study. The remaining 45 patients were counseled either in English or one of the languages spoken by the genetic counselor and clinical geneticist (Bahasa Malaysia/Malay, Mandarin or Cantonese). The genetic counselor conducted a telephone survey and intake interview. If the patient expressed interest to know the outcome of their test results, she was invited to attend a genetic counseling session with a clinical geneticist and genetic counselor. The counseling session included provision of brief information about familial breast cancer and the BRCA1 and BRCA2 test, in-depth examination of the family history, result disclosure and explanation of the implications of a positive result, including inheritance and risk to family members, and provision of support for the individual. Follow-up letters were sent to the patients and patients were referred back to their attending clinician (the breast surgeon) for further clinical management. The results of the test were released with consent from the patients.

Results

Provision and acceptance of genetic counseling in index patients

All 49 patients who had deleterious mutations were approached and offered genetic counseling (Fig. 1). Four patients have since died or were lost to follow up. Of the remaining 45 patients, 37 patients (82%) patients accepted
the offer to attend a genetic counseling session, of which 29, 7 and one patient accepted at the first, second and third telephone call, respectively. The median age of these carriers was 45 years (range 24–64). Eight patients (18%) decided not to have genetic counseling and did not want to find out about their test results. The reasons cited are listed in Fig. 1. Of the 45 index patients who had deleterious mutations in one of the two BRCA genes, 9 were Malays, 10 were Indians and 26 were Chinese. Of the 37 index patients who accepted genetic counseling, 6 were Malays, 8 were Indians and 23 were Chinese (Table 1). Amongst these index patients, English was the most common language used (42%), followed by Cantonese (30%), Malay (14%) and Mandarin (14%).

During the genetic counseling sessions, we found four significant challenges in conducting risk assessment. Firstly, although a large proportion of clients (33% of index patients and 51% of first-degree relatives) had at least college education, there was limited understanding about cancer, genetics and genetic testing and therefore, a substantial part of the counseling sessions was used to explain the basic information.

Secondly, there were major gaps in the patients’ perception of the impact of family history on risk. All index patients reported a different pedigree compared to when they were recruited into the research study. Thirdly, we found that risk assessment was compromised by inaccurate reporting of large families and polygamy and polyandry in

Fig. 1 Results of patients recruited for breast cancer study
families. Many of the families in the cohort were large, thereby making risk assessment complicated by cancers that occur in half-siblings and relatives in polygamous or polyandrous relationships. Five patients (14%) had 1 to 5 first-degree relatives, 18 patients (50%) had 6 to 10 first-degree relatives and 14 patients (36%) had 11 to 15 first-degree relatives. In addition, 27 patients (73%) have more than 15 second-degree relatives. Thirteen patients (35%) were from polygamous (9 patients) or polyandrous (4 patients) families.

Finally, we faced major challenges in the verification of cancer history in Malaysia, in part because there is no complete cancer registry to confirm diagnoses and no complete death registry to confirm cause of death. There was limited verification of pathology reports if the cases were not treated at University Malaya Medical Centre.

Provision and acceptance of genetic counseling in relatives

All first-degree relatives were offered free genetic counseling and predictive testing as part of the research protocol. Of the 37 index patients who were provided with results disclosure, 29 (78%) informed their first-degree relatives about their test results within 6 months of being counseled (Fig. 1). These 29 index patient who informed their families had 471 living first-degree relatives, aged 21 years or older (227 females and 244 males). The testing rate among all relatives was 11% (15% in females and 8% in males). These relatives were from only 18 (62%) families. Of the 61 first-degree relatives that were counseled, 11 were Malays, 8 were Indians and 42 were Chinese. For these first-degree relatives, English was the most common (43%), followed by Cantonese (36%), Malay (18%) and Mandarin (3%). The average interval between the counseling session for the index patient and the first-degree relative coming forward is 3 months (range 1–6 months). First-degree relatives from 4 families are still considering genetic counseling and first-degree relatives from 7 families have declined. The reasons cited for declining genetic counseling are listed in Fig. 1.

Relatives from eleven of the 18 families (61%) who came forward for genetic counseling requested group counseling. In these circumstances, we proceeded with group counseling first, followed by a separate counseling session with each individual. In 6 of the 11 families, group counseling was reported by the relatives to be helpful. Despite care taken to emphasize to the relatives that genetic testing should be an individual decision, in 5 of the families, 8 members felt that there was significant family pressure to be tested with loss of autonomy. We noted some distress in our follow-up for 5 of the first-degree relatives. Three first-degree relatives from 2 families have voiced their concerns about knowing their carrier status and have decided not to proceed with the result disclosure. Two first-degree relatives from another family who tested positive were visibly distraught at result disclosure and have voiced their regret at having proceeded with the test. Three first-degree relatives faced pressure from their parents to conceal their carrier status from their future spouses.

We found that a significant proportion of index patients and their relatives were concerned about passing on the mutation to their children. Of the eleven index patients and 27 first-degree relatives who were under the age of 40 years old and were in their child-bearing years, 14 (52%) were concerned about the possibility of passing on the mutation to their children and 8 (21%) asked about prenatal diagnosis (PND) and pre-implantation genetic diagnosis (PGD) for \textit{BRCA1} and \textit{BRCA2}. Six of the 14 index patients (43%) who had adult children were concerned about passing on the mutation to their grandchildren and asked about PGD for their children.

Uptake of risk management strategies in index patients and relatives

Of the 37 affected index patients and 10 affected relatives, 45 (96%) were already undergoing annual routine breast checkups, but only 10 (27%) had ever attended any check-up
for risk management of gynecological cancers. Of the unaffected relatives, 7 were female. Of these, 2 were undergoing annual routine breast checkups and none had ever attended any check-up for risk management of gynecological cancers. All these patients have subsequently been referred to a multi-disciplinary team that has been established for risk management of breast and gynecological cancers.

**Discussion**

This study has provided data and some insight into the challenges to cancer genetic counseling in Malaysia, depicting the influence of social and cultural backgrounds and the challenges that stem from limited awareness about genetics and familial risk, limited resources for accurate risk assessment and limited regulatory and societal protection against genetic discrimination in a developing Asian country.

Counseling for index patients

This study showed 82% of patients chose to learn their genetic test results. This was higher than a similar study done in Australia where patients were first recruited to a research study and later offered the option to learn their results—only 44% chose to learn their results [24]. However, fewer patients (78%) chose to tell their first-degree relatives compared to other studies (84–95%) [25].

During the genetic counseling sessions, significant linguistic challenges and knowledge barriers were found. The patients in this cohort spoke and understood different languages and dialects. This indicated that genetic professionals ought to be conversant in the languages used in the community where they operate. In some areas, the literacy rates are limited and it is expected that genetic professionals may opt for less detailed information-giving in favor of providing support and empathy for the affected families. We found that there was limited understanding about cancer and genetic testing. Therefore, a substantial part of the counseling sessions was used to explain the basic information. Clients and families appreciated hand-drawn and written genetic information which they can take home with them and share with their family members. This study highlights the need for validated tools to communicate complex genetics knowledge in a culturally sensitive manner.

Genetic counseling in this Asian population faced significant challenges in conducting risk assessment. Firstly, there were major gaps in the patients’ perceptions of the impact of family history on risk, and all index patients reported a different pedigree at the genetic counseling session compared to when they were initially recruited into the research study. This may be due to the availability of professionals trained in genetic counseling in obtaining the pedigree but may also reflect the observation that non-white women are less likely to have their family histories documented than white women [26]. The use of a structured questionnaire in obtaining family history may be useful in this respect [27, 28]. Secondly, we found that risk assessment was compromised by complex family dynamics (including large families, polygamy and polyandry). Thirdly, we faced major challenges in the verification of cancer history in Malaysia as there is no complete cancer registry to confirm diagnoses and no complete death registry. Finally, we note that risk assessment has to date focused largely on data derived from Caucasian multiple-cancer families and it is unclear to what extent this is applicable to an Asian populations with lower breast cancer rate. Taken together, our findings suggest that in order for underserved populations to benefit from genetic counseling and testing, we urgently need better tools to accurately assess risk.

Counseling issues for relatives

Despite having genetic counseling and testing being offered free of charge, only 78% of index patients informed their families about the genetic test. Of these, only 62% of families and 13% of living first-degree relatives came forward for genetic counseling. This study identified a large cohort of individuals at risk for HBOC, consisting of 471 first and second degree relatives from 18 families alone. There is an urgent need to address this issue and to increase the capacity building of the healthcare system by training more genetic counselors and clinical geneticists to cope with this need.

There is currently no regulatory protection against genetic discrimination in Malaysia and in many developing countries. Many clients felt that the fear of discrimination and social stigmatization overrode the perceived risk of developing cancer. In many Asian cultures, family support is vital in decision-making, particularly in difficult medical issues. However, these ‘Eastern values’ of emphasizing societal cohesion and harmony are considered to be detrimental to an individual’s rights of confidentiality, privacy and the right to make informed choices. In our study, the relatives of 10 families wanted to have the support of one another during the counseling session, but this gave rise to a certain amount of ‘coercion’ to have the predictive testing. Taken together, our results suggest that cascading currently has its limitations in Asian breast cancer families and further work is necessary to develop more effective strategies for family communication and testing behaviors.
Main concerns raised by clients

The main concerns expressed by index patients are regarding their risk to develop contralateral breast cancer, ovarian cancer and other cancers, transmission of the BRCA1 or BRCA2 mutation to their children and grandchildren, and social stigmatization. Many patients were not aware of the risk for ovarian cancers. There is a need to improve clients’ awareness regarding the need for surveillance of gynecological cancers in our cohort.

We report concerns regarding genetic guilt and genetic blame: 39% of our clients who were in child-bearing ages (<40 years old) were concerned about passing the mutation on to their children. Twenty percent of clients who were in child-bearing ages and 43% of clients who had adult children asked about availability of PND and PGD, respectively. Some felt that this information was critical in their decision on whether or not to inform their children regarding the results of the genetic test. It is important to note that requests for prenatal diagnosis for conditions such as hereditary cancers that do not affect the intellect and have some treatment options available may engender a range of opinions among medical professionals and within families regarding their use for consideration of termination of pregnancy. Although genetic counselors would consider decisions about these prenatal diagnoses to be the informed choice of the parents, careful discussion of these issues is appropriate during GC. Studies in other countries had shown that genetic testing results do influence individual’s decision on child-bearing, PGD, PND and termination of pregnancy [29, 30].

Our study showed that the clients and their families expressed concerns about genetic testing because they perceived social stigmatization against their family members [31] and how these would affect their chances of finding a partner in life. This social risk was perceived by seven families to be a bigger risk than the health risk of being a carrier. In many Asian cultures, family dynamics involving family pride (‘face’), parental pressures as well as elders’ opinions play a major role in the selection of one’s life’s partners. Any perception that an individual is genetically inferior may result in stigmatization and discrimination by an entire community. Indeed, our study showed some first-degree relatives faced pressure from their parents to conceal their carrier status from their future spouses. It is anticipated that these issues will be important areas for further research in developing countries.

In summary, genetic counseling in HBOC has the potential to further reduce disparities in cancer care, improve survivorship from interventions such as identifying early at-risk individuals for cancer surveillance, risk reduction surgeries and the availability of PND and PND for young families. A large cohort of individuals at-risk for HBOC from family studies was identified. Empowering these at-risk individuals who hitherto had no access to information of their risks has the potential to reduce cancer mortality and morbidity in developing countries. With familial cancers accounting 5–10% of all cancers, genetic counseling as part of a cancer genetic service could potentially leave a huge impact on healthcare indices and health economics on a global scale, as hereditary cancers affect the most productive segment of the population.

We showed this integrated approach to genetic counseling in HBOC is practical and feasible in a developing country. The major limitation of this study is the relatively small number of families available. However, we believe that our cohort is representative of the Malaysian population and the findings are applicable to the majority of the Asian population. Further studies are urgently required to validate these findings in other parts of the world and other hereditary cancers.

Acknowledgments The study was approved by the University Malaya Medical Centre Ethics Committee and all participants gave informed consent before taking part in the research. This study was funded by the Ministry of Science, Technology and Innovation, University Malaya and Cancer Research Initiatives Foundation. The study funders did not have any role in the study design; collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Conflict of interest All authors declare that the answer to the questions on your competing interest form are all “No” and therefore have nothing to declare.

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