Risk factors for ovarian cancer and early-onset breast cancer in Mongolia

L. Elit[1,2], G. Baigal[3], E. Jack[2], A. Munkhtaivan[3], S. A. Narod[2]

[1]Department of Obstetrics and Gynecology, McMaster University
[2]Centre for Research in Women's Health, Toronto (Canada)
[3]National Oncology Hospital, Ulaan Baator (Mongolia)

Summary

Objective: To determine if there are founder BRCA 1 mutations in the Mongolian population.

Methods: Seventeen women with ovarian cancer, 14 women with premenopausal breast cancer and one woman with both cancer types were interviewed to obtain family history, and hormonal, reproductive and environment risk factor information. Blood was collected for DNA analysis from these women to determine the frequency of BRCA1 and BRCA2 mutations in Mongolia.

Results: Two patients had two first-degree relatives with cancer and nine women had one first degree relative with cancer. Two women had the unique BRCA 1 mutation previously described. These two women were not related but their parents were from the same tribe and they lived in the same imak (province). Only one other patient was of this tribal background and from the same region; however, she did not have the BRCA1 mutation.

Conclusion: A substantial proportion of Mongolian woman with ovarian cancer or early-onset breast cancer may be due to a founder BRCA1 mutation 3452delA.

Key words: Ovarian cancer; Breast cancer; Risk factors; Mongolia.

Introduction

Mongolia is a landlocked country with a population of 2.3 million people. Half of the population resides in urban centres and the remainder are nomadic. The National Oncology Hospital in Ulaan Baator provides cancer services for the entire population. The six leading causes of cancer in Mongolia in 1997 were liver (n=151 cases), stomach (n=147), cervix (n=132), lung (n=106), breast (n=65) and esophagus (n=60). From 1997 to 1999, there were 202 new cases of breast cancer. The annual incidence is constant and roughly one-half of the cases occur in the premenopausal age group. Ovarian cancer is the second most common gynecologic cancer in Mongolia. The annual incidence of ovarian cancer is rising; there were 31 new ovarian cancers in 1997 compared to 16 cases in 1990. Approximately 20% of cases occur in each ten-year group from 20-70 years [1]. This age distribution is in contrast to the advanced age of presentation for ovarian cancer in North America. The young age of ovarian and breast cancer in Mongolia, the distinct genetic makeup of the people and their geographic isolation suggest that genetic factors may be important.

In 1999, a 29-year-old Mongolian woman with Stage 4 adenocarcinoma of the ovary was found to carry a previously unreported BRCA1 mutation on exon 11 (3452delA) [2]. To determine whether this finding was specific to this single Mongolian family, or if it was a founder mutation related to an isolated genetic pool, we did genetic testing for BRCA1 and BRCA2 in unselected women with ovarian and early onset breast cancer in Mongolia.

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Methods

Over a six-month period, the National Oncology Hospital oncology staff informed living Mongolian women who had been diagnosed with ovarian cancer or premenopausal breast cancer about a 2-week clinic for genetic testing. The women completed an informed consent. They underwent an interview addressing family history, hormonal, reproductive and environmental risk factors. The interview was conducted in Mongolian but the information was transcribed in English. The hospital charts of women with cancer were reviewed to determine tumor histology, grade, and stage of disease. All the information was entered onto an Excel database.

Blood for DNA analysis was obtained from the cases. The DNA analysis was completed in Toronto, Canada. Genomic DNA was extracted from whole blood using the Puregene DNA Isolation Kit manufactured by Genta Systems. Exon 11 of BRCA1 (in three fragments), and exon 10 (in one fragment) and 11 (in two fragments) of BRCA2 were amplified by standard PCR protocols. The PCR product was used to perform the protein truncation test. The protein truncation test, using the Promega TNT Coupled Reticulocyte Lysate System, was used to screen for truncating mutations in the above exons. The proteins were analyzed by 10.5% denaturing SDS-PAGE for exons 11 of BRCA1 and BRCA2 and 12% SDS-PAGE for exon 10 of BRCA2. The truncated protein band was visualized using Kodak Biomax MR X-ray film. Approximately 92% of BRCA1 exon 11, 72% of BRCA2 exon 10 and 93% of BRCA2 exon 11 are covered using this method. Aberrant bands were detected in the exon of BRCA. Upon manual sequencing of the DNA using Amersham Pharmacia Biotech's (Baie J'Urfe, Quebec, Canada) Thermo Sequenase Radiolabelled Terminator Cycle Sequencing kit and the above-mentioned film, the truncated mutation was revealed.

Results

Thirty-two women with ovarian or premenopausal breast cancer were interviewed. Fourteen women had premenopausal onset of breast cancer, 17 had ovarian cancer and one case had both ovarian and breast cancer.

The cancer population from which these cases are drawn is outlined in Table 1. The characteristics of the cases are outlined in Table 2. All the women with breast cancer had discovered the breast mass themselves. In most cases, the treatment for breast cancer was surgery followed by tamoxifen use (1-3 months) and then ovarian ablation. The ovarian cancer patients were all treated with hysterectomy, bilateral salpingo-oophorectomy with or without omentectomy.

The risk factor questionnaire indicated that the average weight was 60.7 kg (range 20-95 kg). The average height was 149.5 cm (range 140-167 cm). There was poor recall for birth weight and the weight at age 30 and 40 years. Three of the women with ovarian cancer smoked between 0.5 and 1 package of cigarettes per day. Two of these women had smoked for 40-50 years. Five women drank alcohol socially. Two women had other medical problems (renal disease, arthritis). There were no other coexisting malignancies aside from breast and/or ovarian cancer.

Twenty-one patients had no family history of cancer, nine patients had one first degree relative with cancer and two patients had two first-degree relatives with cancer. There was no history of breast cancer in the relatives. The types of cancers found in the first degree relatives were stomach (4), liver (3), ovary (2), head and neck (2), lymphoma (1), and primary of unknown origin (1). Geographically, the parents of women with cancer represented 70% of the imaks (or provinces) in Mongolia.

All 32 women underwent BRCA testing. Two unrelated individuals with ovarian cancer were found to carry the same BRCA 1 mutation on exon 11 (3452delA). No mutations were found in women with breast cancer. The women with mutations developed ovarian cancer, at 29 and 60 years, respectively. The proportion of women with ovarian cancer and a mutation is 11.8%. Interestingly, both women had maternal and paternal roots in the darganga tribe. The parents of both women came from Sukhabaatar imak. The family history of the 29-year-woman has been described previously [2]. The 60-year-old woman was an only child. She had seven children.

Table 1. — *1997-1999 age-specific occurrence of breast or ovarian cancer, National Oncology Hospital, Ulaan Baator, Mongolia.*

	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	>60	Total
Breast Cancer										
Population	3	8	10	24	32	28	28	25	44	202
Study			4		4		1		1	10 (5%)
Ovarian Cancer										
Population	10	3	7	8	7	5	8	8	24	86
Study	1		1	1	3				6	12 (14%)

Table 2. — *Characteristics of the population.*

Factors	Cases No. = 32
Age	
Mean	46.53 yr
Range	20-79 yr
Pregnancy	
Number of women	32 (100%)
Mean	5
Range	1-12
Breast feeding	
Number who breast fed	30 (93.75%)
Mean duration of breast feeding	64 mos
Menarche	15 yr
Infertility	3 (9%)
OBCP use	3 (9%)
Tubal ligation	1 (3%)
Prior gynecologic surgery	9 (28%)
Prior abdominal surgery	7 (22%)
Smoker	3 (9%)
Coffee use	14 (44%)
Alcohol	5 (16%)
Hayfever	0
Asthma	3 (9%)
Eczema	2 (6%)
Mean number of first degree relatives	10.6
Mean number of first degree relatives with cancer	0.31
Range	0-2
Number patients with 2 first degree relatives having cancer	2
Number of patients with 1 first degree relative with cancer	9
History of Ovarian Cancer	15 (46.88%)
History of Breast Cancer	18 (56.25%)
Date of diagnosis	
Ovarian cancer	1985-2000
Breast cancer	1992-2000

None of her first degree relatives had cancer. There were two women with breast cancer from the Sukhabaatar imak; one also came from the darganga tribe. Neither had a genetic mutation.

Discussion

Unique mutations may be specific to a family or they may arise and be propogated in geographically isolated populations [3]. Founder effects have been described in populations from Israel [4-14], Holland [15, 16], French Canada [17, 18], Russia [19], Italy [20-22], Iceland [23-25], Japan [26, 27], Germany [28, 29], Finland [30], Sweden [31], France [32], Hungary [33] and Africa [34]. We previously described a unique BRCA1 exon 11, 3452delA mutation in a Mongolian family. In this study, two Mongolian women with ovarian cancer carry this mutation. Interestingly, both patients have genetic roots

Table 3. — *Characteristics of the population.*

Mean Age	Ovarian Cancer 49.1 (Range 20-77)	Breast Cancer 49 (Range 30-66)
Stage	1A - 5 1B - 2 2C - 1 3C - 7 Unknown - 3	0 - 1 1 - 1 2 - 7 3 - 2 4 - 2 Unknown - 2
Histology	Serous - 10 Mucinous - 1 Endometrioid - 1 Unclassified - 6	CIS - 1 Ductal - 3 Lobular - 1 Tubular - 3 Unclassified - 2 Unknown - 5
Clinical		Right - 6 Left - 9
Primary	Surgery alone - 2 Surgery with cisplatin - 16	Oophorectomy - 4 Ovarian Radiation - 7 Tamoxifen - 10 (1-3 months) Chemotherapy - 1

in the same tribe and their families originate in the same region of the country.

This study does not represent population-based genetic testing or random testing of cases with ovarian or premenopausal breast cancer. Cases that were more likely to undergo testing were those women who resided near the cancer hospital or who were currently undergoing treatment because it was easier for them to access the 2-week genetic clinic. Women with ovarian cancer were more likely to hear about the genetic clinic because the study organizers were from the Division of Gynecologic Oncology. To obtain a more representative sample of the Mongolian population and a larger sample size, testing of all new cases of ovarian or premenopausal breast cancer could be conducted using buccal swabs as the transport of blood products internationally is problematic.

An age-matched control group would be required to assess the importance of the reproductive and environmental factors. It is interesting that half of the women in this group had had a miscarriage and a quarter of the early-onset breast cancer cases had had a first trimester therapeutic abortion. Large case-control studies have not shown induced or spontaneous abortions to be a risk factor for breast cancer [34-38].

Given that the average monthly household income in Mongolia is $ 40 USA funds, mapping of the entire gene is not an option for most women with a family history of ovarian or early-onset breast cancer. In our hands, testing for a single mutation costs approximately $ 25 USA which is an option in a setting where a founder effect is known. Given the unique BRCA1 mutation that is seen in women especially from the eastern part of the country or from the darganga tribe, the possibility of single gene testing is more practical. Genetic testing could help guide those women with a family history of ovarian cancer regarding preventative maneuvers such as prophylactic oophorectomy, tubal ligation or birth control pill use.

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Address reprint requests to:
LAURIE ELIT, MD
Hamilton Regional Cancer Centre
699 Concession Street,
Hamilton, L8V 5C2 Ontario (Canada)