

MEETING ABSTRACTS

Open Access

Annual Conference on Hereditary Cancers 2010

Szczecin, Poland. 25-26 November 2010

Edited by Jan Lubiński

Published: 12 January 2012

These abstracts are available online at <http://www.hccjournal.com/supplements/10/S1>

MEETING ABSTRACTS

A1

Large genomic rearrangements in BRCA1 and BRCA2 genes in breast and ovarian cancer families in Poland

Helena Bielecka^{*}, Bohdan Górski
International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland
Hereditary Cancer in Clinical Practice 2012, **10(Suppl 1):A1**

Mutations in the BRCA1 and BRCA2 genes predispose women to breast and ovarian cancer. The large majority of the alterations identified in these genes are point mutations and small insertion/deletion. However, an increasing number of large genomic rearrangements are being identified, especially in BRCA1. To date 161 and 39 gene alterations have been described in the literature, approximately for BRCA1 and BRCA2. Just few large genomic rearrangements of BRCA1 gene have been reported in Poland.

Technical limitations of conventional PCR-based methods are cause that gross rearrangements can be overlooked. It has been suggest that about 30% of mutations in the BRCA1 gene are missed by standard mutation detection methods. We use Multiplex Ligation-dependent Probe Amplification (MLPA) to analyze BRCA1/2 rearrangements in 300 unrelated patients with strong family history of breast and/or ovarian cancer negative for BRCA1 Polish founder mutation.

The purpose of this study is establish the prevalence of BRCA1 and BRCA2 large genomic rearrangements in patients with hereditary breast and/or ovarian cancer of Polish population.

A2

Spectrum of tumors in the families with Hereditary Breast Ovarian Cancer syndrome carrying germline mutations in BRCA1 and 2 genes

M Budryk^{1*}, J Pamula-Pilat², K Tęcza², E Grzybowska²
¹Genetic Counseling In Outpatient Clinics, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland; ²Center for Translational Research and Molecular Biology of Cancer, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland
E-mail: magda.budryk@op.pl
Hereditary Cancer in Clinical Practice 2012, **10(Suppl 1):A2**

The aim of genetic tests performed by Genetic Counseling at Centre of Oncology was to screen for carriers of germline mutations in BRCA1 and 2 genes who are at high risk of developing breast or/and ovarian cancer.

Among the patients qualified to genetic tests there are the patients who do not meet the Amsterdam criteria of HBOC syndrome.

In Genetic Counseling at Centre of Oncology we find germline mutations in BRCA1 and 2 genes in about 5% of patients. Beginning in January 2003 until now we found mutations in BRCA genes in 247 families. Not all families belong to the group of high risk of developing breast or ovarian

cancer. Among them there were 23 families which did not meet pedigree and clinical criteria.

Analysis of tumors which were developed by the members of families carrying germline mutations in BRCA1/2 genes revealed mainly breast (415) and ovarian (170) cancers. There were also tumors which were not typical for this mutation. The most frequent not typical tumors in the families with germline BRCA1/2 mutations were: lung cancer (38), intestinal tract tumors (26) – including stomach cancer, liver cancer (20), pancreas cancer (15) and also hematopoietic tumors – among them leukemias (17), prostate cancer (14) and other.

These findings justify performing genetic tests for germline mutations in BRCA1/2 genes not only for the patients who meet pedigree and clinical criteria typical for HBOC syndrome.

A3

Artificial neural network in predicting bladder cancer recurrence

Edyta Borkowska^{1*}, Maria Constantinou¹, Adam Jędrzejczyk², Magdalena Traczyk¹, Monika Banaszkiewicz¹, Michał Pietrusiński¹, Piotr Marks², Marek Roźniecki³, Andrzej Kruk⁴, Bogdan Kałużewski¹

¹Department of Clinical Genetics, Medical University of Lodz, Poland;

²Department of Urology, Medical University of Lodz, Poland;

³Urologists "Marek Roźniecki and Partners", Lask, Poland; ⁴Department of Ecology and Vertebrate Zoology, University of Lodz, Poland

E-mail: edyta.borkowska@umed.lodz.pl

Hereditary Cancer in Clinical Practice 2012, **10(Suppl 1):A3**

Introduction: The more we learn about human genetics and human variation, the more apparent it becomes that our individual make-up has a noticeable impact on the effectiveness of medications. Urinary bladder cancer is the sixth leading cause of mortality due to malignant neoplasm among Polish man in Lodz region. Many genetic and epigenetic alterations have been identified that contribute directly to the development of bladder tumors. The aim of the project was the creation of the individual risk calculator of bladder cancer recurrence using available clinical data and the results of the long term genetic research.

Material and methods: Experimental molecular markers (including P53 and CDKN2a mutations and polymorphisms, assessment the level of genes expression, loss of heterozygosity), UroVysion test results, HPV infection status and conventional clinicopathological data were studied in a cohort of 104 patients (92 men) with bladder cancer diagnosed between November 2006 and June 2008 (the mean age was 67). 44 lesions were determined to be non-invasive tumors (pTa), whereas 36 were invasive (pT1-T4). Tumor grade was noted low (G1) in 46 cases and high (G2-3) in 34 cases. For modeling the relationship between the explained variable (time without recurrence) and explaining variables a multilayer perceptron was used (a kind of artificial neural network). Its functioning can be compared to how the so called "black box". We know what data are introduced, we are acquainted with the obtained result, however we have no knowledge of what process takes place inside.

Results: The predicted variable was coded as follows: 0-high risk of recurrence and death, 1- early recurrence, 2-late recurrence, 3- very low risk for recurrence. Next, the set of data was divided into three sub-groups: training (65 cases), validation set (20 cases) and test set (19 cases). The fact that artificial neural networks create models of phenomena only on the basis of representative data previously gathered by investigators is useful in several aspects. Firstly, for using artificial neural networks a priori knowledge of the problem in the statistical sense is not required. Secondly, the construction of the model may result in identification of new important variables, which possibly would be ignored using conventional statistical analysis. Thirdly, it should be noted that the artificial neural networks are able to deal with lack of data, the problem which often encountered in clinical practice.

Conclusion: The calculator proposed by us takes into considerations clinicopathological, genetic and environmental data (like tobacco smoking and occupational exposure). To our knowledge this is first attempt to include a various genetic variable into the bladder cancer recurrence calculator. We intend to increase the amount of data presented to the net so the process of net training can be more effective and it can allow calculating the risk of disease progression. In our opinion this is the direction which should be followed, especially in the oncoming era of personalized healthcare and individual therapy.

A4

Why choose the treatment with cisplatin for BRCA1 breast cancers patients?

T Byrski¹, T Huzarski¹, E Marczyk¹, P Blecharz², J Gronwald¹, O Ashuryk¹, C Cybulski¹, T Dębniak¹, D Zuziak³, D Godlewski⁴, J Kladny¹, J Lubinski¹, SA Narod⁵

¹Pomeranian Medical University, Szczecin, Poland; ²Oncology Institute, Kraków, Poland; ³Regional Oncology Center, Bielsko-Biała, Poland; ⁴Center for Epidemiology and Prevention, Poznań, Poland; ⁵Women's College Research Institute, Toronto, Ontario, Canada
E-mail: tomekbyr@poczta.onet.pl

Hereditary Cancer in Clinical Practice 2012, **10(Suppl 1):A4**

Purpose: To identify host and tumor factors which predict a complete pathologic response (pCR) after neoadjuvant treatment with cisplatin chemotherapy in women with breast cancer and a BRCA1 mutation.

Patients and methods: 50 women with breast cancer and a BRCA1 mutation, who presented with stage I to III breast cancer between December 2006 and April 2010 were enrolled and treated with cisplatin 75 mg/m² every three weeks for four cycles, followed by mastectomy and conventional chemotherapy. Eight patients had prior chemotherapy for a previous cancer diagnosis. Three patients received prior chemotherapy for their current cancer diagnosis but received protocol therapy and thus were followed for toxicity and evaluated for response. Information was collected on clinical stage, grade, hormone receptor status and Her2neu (HER2) status prior to treatment. Pathologic complete response was determined by review of surgical specimens.

Results: 47 patients were enrolled in the study, including 39 patients for whom this was the first primary breast cancer and who had no previous chemotherapy and 8 patients who had previously received chemotherapy. A pathologic complete response (pCR) was observed in 34 patients (68%) including 82% of women who had no previous chemotherapy and 18% of women who had previously received chemotherapy.

Conclusions: Platinum-based chemotherapy is effective in a high proportion of patients with BRCA1-associated breast cancer, but may be less effective in women who have been previously been treated with another form of chemotherapy.

A5

The risk of breast cancer in women with a CHEK2 mutation

Cezary Cybulski*, Dominika Wokolorczyk, Anna Jakubowska, Tomasz Huzarski, Tomasz Byrski, Jacek Gronwald, Tadeusz Dębniak, Bohdan Górski, Steven A Narod, Jan Lubiński

International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland
E-mail: cezarycy@sci.pam.szczecin.pl

Hereditary Cancer in Clinical Practice 2012, **10(Suppl 1):A5**

Mutations in CHEK2 predispose to a range of cancer types including breast cancer. A meta-analysis of all association studies estimated the risk of breast cancer among carriers of 1100delC to be increased by 2.7-fold (9) and increased by 4.7-fold among carriers with a positive family history of breast cancer (Weischer M et al. CHEK2*1100delC genotyping for clinical assessment of breast cancer risk: meta-analysis of 26,000 patients cases and 27,000 controls. *J Clin Oncol* 2008; 26: 542-548). We estimated the risk of breast cancer in a woman who has a CHEK2 mutation depending on her family history of breast cancer. Our data suggest that carriers of a truncating mutation of CHEK2 (IVS2+1G>A, del5395, 1100delC) have 2.9 – fold increased risk of breast cancer in the Polish population. The risk was higher for women with at least one first-degree relative with breast cancer (OR = 4.5), and for women with at least one second-degree relative with breast cancer (OR = 3.5). If both a first- and second-degree relative was affected with breast cancer, the odds ratio was 6.4. We estimate the lifetime risks for carriers of CHEK2 truncating mutations to be from 21 to 37% depending family history of breast cancer in first- and second degree relatives. CHEK2 mutation screening detects a clinically meaningful risk of breast cancer.

A6

Clinical genetics of melanoma

T Dębniak

International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland
E-mail: debniak@sci.pam.szczecin.pl

Hereditary Cancer in Clinical Practice 2012, **10(Suppl 1):A6**

Malignant melanoma (MM) represents one of the most aggressive neoplasms and its frequency is increasing rapidly. Increased melanoma risk among relatives of MM patients and familial aggregations of this malignancy point at genetic predisposition as an important factor of MM pathogenesis. The genetic basis of MM is complex and appears to involve multiple genes. CDKN2A is regarded as the major MM susceptibility gene. In the Polish population common CDKN2A variant (A148T) increases significantly melanoma risk regardless of the cancer family history. Mutations of other high risk genes, ARF and CDK4 are extremely rare and thus clinically insignificant.

The higher rates of CDKN2A/p16 mutations can be detected only in rare cases characterized by:

- 1) occurrence of three or more primary melanomas,
- 2) patients with three or more melanomas in aggregate among first or second degree relatives,
- 3) families with the presence of three or more cases of melanoma and/or pancreatic cancer on the same side of the family. It is thus necessary to perform association studies focused on identifying genetic markers that could be used in identifying patients with a high risk of MM. List of other genes that carry mutations, which are believed to be associated with moderate MM risk include XPD, MC1R, BRCA2. Newest genome-wide association study identified three loci associated with melanoma risk: 16q24, 11q14-q21, 9p21.

The management with individuals being at increased MM risk involves clinical screening according to carefully planned surveillance schedule and early treatment of MM tumour. The appropriate management may reduce morbidity and mortality. Genetic testing and clinical evaluation should be performed, and family history should be obtained in all patients affected with MM, also in those with apparently sporadic tumors.

A7

Rapid test for detection of high risk of breast cancer

K Durda*, K Jaworska, A Jakubowska, T Dębniak, B Górski
International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland
E-mail: k.durda@onet.pl

Hereditary Cancer in Clinical Practice 2012, **10(Suppl 1):A7**

Direct sequencing of genes is effective method in detection of mutations associated with high predisposition to breast cancer, however is also expensive and time consuming. Therefore, we developed a rapid genetic test for detection of high risk of breast cancer in Polish population. We selected

15 mutations located in four genes associated with high predisposition to breast cancer in Poland: BRCA1 - 5 mutations (Górski et al. IJC 2004) BRCA2 - 5 mutations (Górski et al. IJC 2004, Serrano Fernandez et al. BCRT 2009), CHEK2 - 4 mutations (Cybulski et al. Clin Res. 2006, Cybulski et al. BCRT 2007, Cybulski et al. JMG 2009, Cybulski et al. Clin Genet. 2009, Gronwald et al. BJC 2010) i ATM - 1 mutations (Bogdanowa et al. BCRT 2009).

For genotyping we used the Real-Time PCR technique and custom-made Taqman assays. This test is rapid (results of Taqman genotyping we are available within 2 hours), cheap, easy and sensitive in detection of mutations in genes associated with high predisposition to breast cancer.

In order to meet all sensitivity and quality standards for such tests we are using positive, negative and blinded control in each analysis. The specificity and reproducibility of this test is assessed by repeated analysis of 10% samples. All positive results are confirmed by analysis of second sample from the same patient by independent method eg. PCR-RFLP or sequencing.

A8

Selenium and genotypes as marker of risk in BRCA1 mutation carriers

K Jaworska*, A Jakubowska, T Huzarski, K Durda, P Serrano-Fernandez, G Sukiennicki, M Muszyńska, T Byrski, J Gronwald, S Gupta, J J Lubiński
International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland
E-mail: ka_jaworska@wp.pl

Hereditary Cancer in Clinical Practice 2012, 10(Suppl 1):A8

Aim of the study: Identification of genetic variations in genes related to metabolism of selenium, including glutathione peroxidases (GPX) and thioredoxin reductases (TXNRD) as markers for breast cancer and/or ovarian cancer risks in carriers of BRCA1 gene mutation: analysis of selected changes in the subgroups, depending on the plasma selenium concentration.

Material and methods: A group of 50 newly diagnosed breast and/or ovarian cancer patients carrying BRCA1 mutation was analyzed by exon-by-exon sequencing of 3 genes (GPX1, GPX4, TXNRD2) coding selenoproteins. Simultaneously a nested case-control study of 39 women with breast cancer and 7 women with ovarian cancer (blood samples for all affected carriers were collected before treatment) and 92 controls matched 1 to 2 cases has been conducted and changes detected by sequencing have been analyzed. Additional case - control studies were performed on 45 pairs 1:2 matched for GPX1 (rs1050450). All cases and controls were matched for age at enrolment, past history of breast cancer and oophorectomy. All these patients were carriers of one of three Polish founder BRCA1 mutation. In these patients plasma selenium level has been determined.

The following techniques for laboratory analyses have been applied:

- sequencing on (ABI310),
- SimpleProbe or Taqman analysis (a melting-curve genotyping with fluorescence-labeled probes based on the LightCycler 480 System (Roche Applied Science)),
- determination of selenium concentration in plasma using atomic absorption spectrometer AAnalyst600 (Perkin Elmer).

Results: The strongest association has been found for GPX1 (rs1050450). Multivariate statistics allowed the analysis of each risk factor separately as well as their interaction with the help of logistic regression model. Subjects having plasma selenium levels under or equal 80 µg/l showed a generally decreased risk of being diseased (OR=0.24; 95%CI= 0.06-0.94; p=0.041). The genotype of rs1050450 in the gene GPX1 was not a risk factor for itself (p=0.70). However, when analyzed in combination, an interaction effect could be proven where carriers of the minor allele of rs1050450 having plasma selenium levels above or equal 80µg/l were under an increased disease risk (OR=6.24; 95%CI=1.09-36; p=0.040).

This effect was even more exacerbated among those women which joined the study after adnexectomy (OR=29.2; 95%CI= 1.6-2000; p=0.0076), while among women without adnexectomy the effect could not be detected at all (OR=2.27; 95%CI= 0.30-27.8; p=0.43). Adnexectomy was not a risk factor itself in the logistic regression model (p=0.49). Cases and controls in triplets with the same genotypes of GPX1 were also taken into account. Although no significant result was achieved, there was a tendency for more unaffected subjects of CC genotype-carriers in GPX1 with serum selenium levels above or equal 80µg/l (5:14 instead of expected 5:10). The opposite was shown for non-CC genotype carriers in GPX1 with plasma selenium level above or equal 80µg/l (12:18 instead of expected 12:24).

Acknowledgments: Authors thank Ms. Zdziebło M. and Ms. Bińczak J. for excellent technical assistance.

A9

BRCA1 mutation- oncological treatment- reconstructive surgery of the breast- pregnancy: diagnostic and therapeutic procedures in a 28 year old patient diagnosed with a tumor in the left breast with a BRCA1 mutation

Ewa Kilar

Swidnica, Poland

E-mail: ewakilar@post.pl

Hereditary Cancer in Clinical Practice 2012, 10(Suppl 1):A9

Process of diagnostic procedures (oncological approach): Phase I: Primary diagnosis

1. Fine Needle Biopsy of tumor in left breast number 1666/2007- cellular neoplasm (september 2007).

2. Thick needle biopsy 4.10.2007- indeterminate results.

Phase II: Surgical diagnoses

1. Quadrant resection of left mammary gland with tumor (T2N0Mx) (October 12,2007) histological pathology number 14946 Infiltrative ductal carcinoma (8 points).

Receptor results in neoplastic cells of the tumor in the left breast (October 12, 2007).

Receptors: Estrogen (+) Progesterone (-) Her2/Neu(-).

2. Lymphoscintigraphy (October 25, 2007)- resection of sentinel lymph node (using gamma camera lymph node was located from the left axilla, where isotope was located).

Histopathological results of the sentinel lymph node showed reactive lymphadenitis.

Phase III: Diagnosis after surgery (genetic approach)

Opolskie Center of Oncology ul. Katowicka 66a oraz w MCND PUM w Szczecinie.

1. In family history BRCA 1 mutation in mother who was during treatment of invasive carcinoma of the mammary gland at that time.

2. Patients molecular results- BRCA1 mutation.

Phase IV: Diagnosis after genetic consultation

Gynecological exam, transvaginal ultrasound (11.12.07).

Ultrasound of breast (11.12.07)- left mammary gland, after surgical removal of tumor, neighboring fluid levels 0.4x3.27cm.

Marker CA-125- 11.5 U/ml (11.10.07).

MRI of breast (11.17.07)- neighboring with the surgical scar within left breast medially and anteriorly seen fluid 2x2x2.2cm.

Treatment of patient in a patient with BRCA1 mutation (oncological approach).

Qualified for Cis Platin chemotherapy (4 cycles of Cis Platin- from November to February 2008) before surgery.

Qualified for surgery (03.14.08) performed at the oncological center in Gdansk, profilactic subcutaneous mastectomy of right breast, also subcutaneous mastectomy of left breast (s.p. surgical removal of ductal ca.) simultaneously with reconstruction of both breasts.

After reconstructive surgery of breasts patient was under care of the Oncological Outpatient Clinic that is part of "Latawiec" hospital in Swidnica.

Patient after treatment active in her career: Decision about pregnancy and medical consultation (gynecological approach).

1. October 2009 patient decided to become pregnant and 26 July 2010 had a healthy girl with Down Syndrome (karyotyp 47, XX,+21).

2. During pregnancy patient consulted a gynecologist but did not find a motive to terminate pregnancy.

3. Patient did not have amniocentesis. Program for amniocentesis qualifies patients from age 35.

4. Patient during pregnancy and currently active in her career.

Discussion: New element of oncological treatment was to decide if the use Cis Platin before surgery was the right form of treatment.

Resulted in a esthetic effect after reconstructive surgery of breasts.

It was kept in mind that there could be negative effects during pregnancy (hormonal changes) and after pregnancy in patients gynecological health.

Patient was part of decision making throughout treatment and possibilities of side effects in patient and the child.

Results: Use of Cis Platin as a first choice together with surgical treatment gives beneficial results in treatment of patient with BRCA1 mutation.

It is not clear in what degree the treatment affected the child's development during gestation.

Seems necessary that decides to get pregnant after oncological treatment should undergo amniocentesis, independent of patients age, to prevent possible teratogenic effects in the development of the fetus.

Acknowledgements: Author would like to thank Tadeusz Kobierzycki for methodological consultation.

A10

The CHEK2 GENE mutations and the risk of Gastric cancer

Urszula Teodorczyk^{1*}, Cezary Cybulski¹, Anna Jakubowska¹, Teresa Starzyńska², Małgorzata Ławniczak², Katarzyna Ferenc², Krzysztof Marlicz², Zbigniew Banaszekiewicz³, Rafał Wiśniowski⁴, Jan Lubiński¹

¹International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland; ²Clinic of Gastroenterology, Pomeranian Medical University, Szczecin, Poland;

³Clinic of General Surgery, University Hospital, Bydgoszcz, Poland;

⁴Beskidian Center of Oncology, Bielsko Biala, Poland

E-mail: urteo@pum.edu.pl

Hereditary Cancer in Clinical Practice 2012, 10(Suppl 1):A10

Background and aims: CHEK2 gene is located on chromosome 22q12.1 and encodes the human analogue of the yeast checkpoint kinases Cds1 and Rad 53. Activation of CHEK2 in response to DNA damage prevents the cell from entering into mitosis. Three founder alleles are present in Poland. Two of these result in a truncated CHEK2 protein IVS2+1G>A in exon 3 and 1100 del C in exon 10, the other, I157T is a missense substitution of an isoleucine for a threonine in exon 3. A single founder allele of the CHEK2 has been associated with predisposition to breast and prostate cancer in North America and Europe. CHEK2 alterations are associated with an increased risk of thyroid, prostate, breast, colon and kidney cancer in Polish population. Recently, a large deletion of exons 9 and 10 of CHEK2 was identified in several unrelated patients with breast cancer of Czech or Slovak origin, the del 5395 also confers an increased risk of prostate cancer in Polish men. The CHEK2 is therefore a good candidate for a multisite cancer susceptibility gene. We reasoned, that CHEK2 alterations ought to be investigated in gastric cancer cases, too.

Patients and methods: We have examined the frequency of the CHEK2 gene mutations in a series of randomized individuals including 749 consecutively collected stomach cancer, 166 patients with familial gastric cancer, and 5496 control patients. The 1100 del C, IVS2+1G→A, I 157 T and del 5395 mutations were identified by ASA-PCR, RFLP-PCR, multiplex-PCR.

Results: The frequency of the I157T mutation in a group of consecutive gastric cancer patients was significantly elevated compared to the control population (OR=1.418, p=0.0348), herein in the group of patients diagnosed with disease less than 50 years of age (OR=1.825, p=0.0511). I157T was over-represented in the group of familial gastric cancer patients (OR=2.246, p=0.003) too, herein in patients diagnosed with disease less than 50 years of age (OR=3.171, p=0.0044) and in females (OR=2.973, p=0.0041).

The IVS2+1G>A was over-represented in a group of consecutive patients with gastric cancers (OR=3.367, p=0.002), therein in patients diagnosed under 50 years of age (OR=4.524, p=0.0377) and over 50 years of age (OR=3.034, p=0.0183) additionally in males (OR=3.706, p=0.0041). A large deletion of exons 9 and 10 confers an increased risk of familial gastric cancer in patients diagnosed over 50 years of age (OR=5.922, p=0.0598), but this result is not quite significant.

Conclusions: The CHEK2 I157T mutation may be a predisposing genetic factor associated with both, consecutive and familial gastric cancer risk. Occurrence of IVS2+1G→A alteration confers an increased risk of consecutive gastric cancer.

A11

Prospective observation of breast/ovarian cancer risk in BRCA1 carriers depending on serum selenium level optimized with diet

J Lubiński¹, T Huzarski, A Jakubowska, J Gronwald, K Jaworska, M Muszyńska, G Sukiennicki, K Durda, C Cybulski, T Dębniak, A Tołoczko, O Oszurek, P Serrano-Fernandez, R Scott, S Narod

International Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland

E-mail: lubinski@sci.pam.szczecin.pl

Hereditary Cancer in Clinical Practice 2012, 10(Suppl 1):A11

The aim of the study is to observe prospectively the possibility of lowering the cancer risk among BRCA1 carriers by optimizing selenium concentration in diet/organism. Results of studies performed in several centres, particularly of our own search, are strongly indicating on potential of decreasing breast/ovarian cancer risk among carriers by optimization of selenium concentration in the body. Studies will be performed on group of 1500 BRCA1 carriers. Cohort will be recruited during the first 6 months of the project. Mean length of follow-up will be 3 yrs. From all females serum will be collected for selenium analyses at the beginning and, then, every 6 months. Participants will receive the list of products with selenium concentration estimated according to literature data and, additionally, information about e-store (<http://www.dietaantytrakowa.pl>) specialized in distribution of food products with defined amount of selenium. Information on optimal selenium concentration according to existing data will be provided also. It is expected that among ~750 carriers following recommended diet changes 38 cancers will be diagnosed and among the others ~750-60. The difference between groups will be statistically significant with p=0.0278. If necessary, investigation will be extended.

A12

DNA testing for high risk of prostate cancer

Dominika Wokolorczyk

International Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland

E-mail: dominikawok@o2.pl

Hereditary Cancer in Clinical Practice 2012, 10(Suppl 1):A12

Association studies of candidate genes in DNA repair and cell cycle control pathways identified mutations associated with a susceptibility to prostate cancer in BRCA1, BRCA2, CHEK2, NBS1 and BRIP1 genes. Mutations in these genes confer 1.5- to 6-fold increase in the risk of prostate cancer. In general, the risks associated with these mutations are higher in carriers who report family history of prostate cancer (the risk increased 3- to 15-fold).

Our studies confirm that rare mutations in DNA damage repair genes are associated with a predisposition to prostate cancer. Specific mutations in NBS1, BRCA1 and CHEK2 genes are associated with 1.6- to 4.6-fold increased risk for prostate cancer in the Polish population. The risk is higher, increased approximately 5 - 15 fold, in carriers who report prostate cancer in at least one first and/or second degree relative.

In the past three years, new DNA markers of low penetrance for prostate cancer were identified by GWAS studies. Of these markers, the strongest association with disease risk was seen for markers of chromosome 8q24. We analyzed how markers of this region influence prostate cancer risk in a series of cases and controls from Poland. Single markers of 8q24 were associated with a low penetrance for prostate cancer - approximately 1.5-fold increased risk (ORs ranged from 1.4 to 1.6). Carriers of two different markers had the risk increased on average by 2.5-fold. Carriers of risk alleles of three markers had on average 6-fold increased risk. Carriers of five markers of 8q24 had an odd ratio of 10.7 for prostate cancer (95% CI 3.3 - 36).

A13

Fast diagnostic test for the identification of an increased genetic predisposition to colon cancer (exemplified on a DNA test for recurrent mutations of the gene MMR)

G Kurzawski¹, D Dymerska, J Suchy, T Dębniak, J Lubiński

International Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland

E-mail: gkurz@sci.pam.szczecin.pl

Hereditary Cancer in Clinical Practice 2012, 10(Suppl 1):A13

Hereditary nonpolyposis colorectal cancer (Lynch Syndrome, LS) is a genetic disorder, where family members are at high risk of developing cancer of the colon, endometrium, small intestine and urinary tract. The cause for LS is due to constitutional mutations in several mismatch repair genes (MMR) mainly in *MLH1*, *MSH2* and *MSH6*.

The Polish population has been well characterized by a large study comprising ~1000 LS-suspected families. Most nucleotide substitutions (about 90%) were discovered mainly by DHPLC (*denaturing high-performance liquid chromatography*) or sequencing, whereas deletion of one or more exons (about 10% of all mutations) were detected mainly by MLPA (*multiplex ligation-dependent probe amplification*) [1,2].

Over 60% families of the former study, which were affected by recurrent MMR mutations, were taken as a basis to design the following iPLEX/TaqMan test, that allows simultaneous testing of almost all recurrent mutations in only analysis [3].

The drawback of this kind of analysis are the high costs of the machines (*Sequenom*), for which a reasonable cost-effectiveness is achieved only for large series of probes. Thus the approach is convenient only for high-throughput laboratories.

However the present approach is cost-effective even for testing individual patients. The present test, based on a Taqman PCR analysis, allows a fast identification of the 20 most frequent mutations of the genes *MLH1* and *MSH2*. An analogous test for recurrent mutations of the gene *APC* could, in a similar way, accelerate the molecular diagnostic of predisposition to FAP.

References

1. Kurzawski G, et al: Germline *MSH2* and *MSH1* mutational spectrum including large rearrangements in HNPCC families from Poland (update study). *Clinical Genetics* 2006, **69**:40-47.
2. Suchy J, et al: Frequency and nature of hMSH6 germline mutations in Polish patients with colorectal, endometrial and ovarian cancers. *Clin. Genet* 2006, **70**:68-70.
3. Dymerska D, et al: Combined iPLEX and TaqMan assays to screen for 45 common mutations in Lynch syndrome and FAP patients. *J Mol Diag* 2010, **12**:82-90.

A14

Identification of patients at high risk of negative psychological consequences associated with BRCA1 mutation

S Ertmański^{1*}, K Metcalfe², J Trempała³, M Głowacka⁴, J Lubiński¹, S Narod⁵, J Gronwald¹

¹International Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland; ²Lawrence S. Bloomberg Faculty of Nursing, University of Toronto, Toronto, Canada; ³Department of Psychology of Human Development, Kazimierz Wielki University in Bydgoszcz, Bydgoszcz, Poland; ⁴Department of Health Sciences, Poznań University of Medical Sciences, Poznań, Poland; ⁵Women's College Research Institute, University of Toronto, Toronto, Canada

E-mail: slawekertmanski@wp.pl

Hereditary Cancer in Clinical Practice 2012, **10(Suppl 1)**:A14

Genetic studies of hereditary predisposition to cancer are becoming more accessible and acceptable form of cancer prevention. However, it is suggested that there is a potential impact of diagnosed high risk of developing cancer on the psychological functioning of patients. Research on this subject has been carried out in other countries, while in Poland similar studies using psychological tests have not been conducted so far. The objectives of the research were:

1. psychological assessment of patients before undergoing of genetic test diagnosing high predisposition to breast cancer or ovarian cancer (BRCA1 test),
2. assessment of psychological reactions of patients after receiving of the positive BRCA1 test result,
3. evaluation of the usefulness of selected psychological tests for identification of patients likely to respond by excessive psychological distress to the positive BRCA1 test result.

It was found that the average level of trait anxiety among BRCA1 carriers before receiving the genetic test result was 5.6, and the level of basic hope - 6.0 and these values are within the population standards for these tests. The average level of state anxiety was only slightly above normal - 6.7. There were no differences between female patients suffering from cancer

and healthy ones. The average level of state anxiety measured one month after receiving the genetic test result increases slightly and after a year - drops slightly below the state before the genetic test - both in groups of people suffering from cancer, and healthy ones (although not statistically significant). The negative psychological reaction to an abnormal genetic test result measured by the IES test (post-test1 after one month) is significantly higher in patients with diagnosed cancer compared to healthy subjects ($p=0.0008$). The high level of state anxiety (standard ten: 9 and 10) measured prior to obtaining genetic test result was found in 18% of BRCA1 mutation carriers. Statistically significant correlation has been registered between the level of state anxiety and trait anxiety measured prior to obtaining genetic test result and the level of state anxiety measured after one month ($p=0.00001$) and after one year ($p=0.00001$) and the level of negative psychological reaction ($p=0.0001$) measured by the IES test one month after obtaining a genetic test result. Statistically significant negative relationship has been found between the level of basic hope measured before obtaining a genetic test result and the level of state anxiety ($p=0.01$) and a negative psychological reaction IES ($p=0.003$) measured one month after obtaining a genetic test result. Such a relationship has not been demonstrated with the level of state anxiety measured after a year. One month after receiving of a genetic test result, 96% of BRCA1 mutation carriers (135/141) recommended genetic testing to other women in a similar situation. By one year posttest, practically all patients recommended genetic testing.

Conclusions: 1. BRCA1 mutation carriers do not exhibit increased constitutional predisposition to excessive negative psychological reactions.

2. There are over ten percent of BRCA1 mutation carriers characterized by a particularly high level of anxiety both before and after undergoing a genetic test that can obtain special benefit from specialist psychological care.

3. The mere fact of genetic testing and obtaining positive genetic BRCA1 test result informing about the predisposition to breast and ovarian cancer does not affect the suffering of long-term anxiety and other negative psychological reactions.

4. Patients affected by cancer have a higher level of negative psychological reaction (IES test after one month) than healthy patients.

5. A result of the measurement of state anxiety by STAI X1 test before undergoing BRCA1 test is a good predictor of psychological reactions observed among BRCA1 mutation carriers after obtaining genetic test result.

6. A result of the measurement of trait anxiety by STAI X2 test before undergoing BRCA1 test is a good predictor of psychological reactions observed among BRCA1 mutation carriers after obtaining genetic test result.

7. A result of the measurement of basic hope by BHI-12 test before undergoing BRCA1 test is a moderately good predictor of psychological reactions observed in the short term (one month) after diagnosing a positive genetic test result, but does not fulfill this role in the long term (over one year).

8. BRCA1 mutation carriers, both in short and long term, recommend to undergo genetic testing to women in similar situations.

Cite abstracts in this supplement using the relevant abstract number, e.g.: Ertmański et al.: Identification of patients at high risk of negative psychological consequences associated with BRCA1 mutation. *Hereditary Cancer in Clinical Practice* 2012, **10(Suppl 1)**:A14