High frequency of BRCA1, but not CHEK2 or NBS1 (NBN), founder mutations in Russian ovarian cancer patients

Evgeny N Suspitsin1,4, Nathalia Yu Sherina1, Daria N Ponomariova1, Anna P Sokolenko1,4, Aglaya G Iyevleva1,4, Tatyana V Gorodnova1, Olga A Zaitseva1, Olga S Yatsuk1, Alexandr V Togo1, Nathalia N Tkachenko6, Grigory A Shiyanov6, Oksana S Lobeiko2, Nadezhda Yu Krylova5, Dmitry A Matsko3, Sergey Ya Maximov2, Adel F Urmancheyeva2,5, Nathalia V Porhanova6 and Evgeny N Imyanitov*1,4,5

Address: 1Laboratory of Molecular Oncology, N.N. Petrov Institute of Oncology, St. Petersburg, Russia, 2Department of Gynecology, N.N. Petrov Institute of Oncology, St. Petersburg, Russia, 3Laboratory of Tumor Morphology, N.N. Petrov Institute of Oncology, St. Petersburg, Russia, 4Department of Genetics, St. Petersburg Pediatric Medical Academy; Department of Oncology, St. Petersburg, Russia, 5Department of Oncology, St. Petersburg Medical Academy of Postgraduate Studies, St. Petersburg, Russia and 6Department of Gynecology, Regional Oncological Hospital, Krasnodar, Russia

Email: Evgeny N Suspitsin - suspitsin@hotmail.com; Nathalia Yu Sherina - natalya.sherina@gmail.com; Daria N Ponomariova - rooibos86@rambler.ru; Anna P Sokolenko - annasokolenko@mail.ru; Aglaya G Iyevleva - aglayai@inbox.ru; Tatyana V Gorodnova - gorodnova00@mail.ru; Olga A Zaitseva - zayats_vorchun@mail.ru; Olga S Yatsuk - olga-yatsuk@mail.ru; Alexandr V Togo - a_togo@mail.ru; Nathalia N Tkachenko - gnbxrf2007@yandex.ru; Grigory A Shiyanov - grigoriysochi@yandex.ru; Oksana S Lobeiko - lobeiko-oksana@mail.ru; Nadezhda Yu Krylova - njur71@mail.ru; Dmitry A Matsko - d.matsko@mail.ru; Sergey Ya Maximov - s.maximov@mail.ru; Adel F Urmancheyeva - adaurm@mail.ru; Nathalia V Porhanova - reytingandrey@mail.ru; Evgeny N Imyanitov* - evgeny@imyanitov.spb.ru

* Corresponding author

Published: 25 February 2009
Hereditary Cancer in Clinical Practice 2009, 7:5 doi:10.1186/1897-4287-7-5
Received: 8 November 2008
Accepted: 25 February 2009

This article is available from: http://www.hccpjournal.com/content/7/1/5

© 2009 Suspitsin et al; licensee BioMed Central Ltd.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Background: A significant portion of ovarian cancer (OC) cases is caused by germ-line mutations in BRCA1 or BRCA2 genes. BRCA testing is cheap in populations with founder effect and therefore recommended for all patients with OC diagnosis. Recurrent mutations constitute the vast majority of BRCA defects in Russia, however their impact in OC morbidity has not been yet systematically studied. Furthermore, Russian population is characterized by a relatively high frequency of CHEK2 and NBS1 (NBN) heterozygotes, but it remains unclear whether these two genes contribute to the OC risk.

Methods: The study included 354 OC patients from 2 distinct, geographically remote regions (290 from North-Western Russia (St.-Petersburg) and 64 from the south of the country (Krasnodar)). DNA samples were tested by allele-specific PCR for the presence of 8 founder mutations (BRCA1 5382insC, BRCA1 4153delA, BRCA1 185delAG, BRCA1 300T>G, BRCA2 6174delT, CHEK2 1100delC, CHEK2 IVS2+1G>A, NBS1 657del5). In addition, literature data on the occurrence of BRCA1, BRCA2, CHEK2 and NBS1 mutations in non-selected ovarian cancer patients were reviewed.
**Background**

Ovarian cancer (OC) is a major cause of oncological mortality in females, with a lifetime risk approaching to approximately 1.7%. Poor outcome of OC is largely attributed to the failure to diagnose the disease at early, potentially curable stages; small tumors of the ovary are usually asymptomatic and likely to be missed by routine gynecological examination [1]. Genetic component may play a key role in OC etiology: depending on the country and ethnicity, 5–50% OC cases are attributed to the germ-line heterozygous inactivation of BRCA1 or BRCA2 genes (see additional file 1). Interestingly, while BRCA-related breast carcinomas (BC) are usually strongly enriched by early onset and familial cancer cases, this relationship is less evident for OC. Although the majority of the studies confirm some association between the presence of BRCA mutation and younger patients age (for BRCA1 but not BRCA2) or family history of the disease (see additional file 1), the strength of this trend is not enough to limit BRCA testing by particular categories of OC patients; instead, the OC diagnosis itself is often considered as a sufficient indication for BRCA analysis. Actually, the occurrence of BRCA mutations in randomly recruited OC cases is fairly similar to the estimates, which are obtained in preselected high-risk categories of women with breast cancer [2-41].

In Russia, a significant fraction of early-onset and/or bilateral and/or familial BC cases is caused by founder mutations in cancer genes [42]. Presence of the “founder effect” significantly decreases the costs of the DNA testing, thus relaxing the criteria for patients selection. While distribution of germ-line mutations in Russian breast cancer cases has been studied with sufficient level of comprehension, no systematic analysis has been undertaken yet for ovarian cancer. Furthermore, breast cancer in Russia and some neighboring countries is caused not only by mutations in BRCA genes but also by heterozygous inactivation of the CHEK2 and NBS1 [42]. It remains unclear, whether the latter 2 genes contribute to OC predisposition as well, or, vice versa, their impact is limited by breast cancer risk.

**Results**

BRCA1 5382insC allele was detected in 28/290 (9.7%) OC cases from the North-West and 11/64 (17.2%) OC patients from the South of Russia. In addition, 4 BRCA1 185delAG, 2 BRCA1 4153delA, 1 BRCA2 6174delT, 2 CHEK2 1100delC and 1 NBS1 657del5 mutation were detected. 1 patient from Krasnodar was heterozygous for both BRCA1 5382insC and NBS1 657del5 variants.

**Conclusion:** Founder BRCA1 mutations, especially BRCA1 5382insC variant, are responsible for substantial share of OC morbidity in Russia, therefore DNA testing has to be considered for every OC patient of Russian origin. Taken together with literature data, this study does not support the contribution of CHEK2 in OC risk, while the role of NBS1 heterozygosity may require further clarification.

**Materials and methods**

Ovarian cancer cases were collected in 2 geographically distinct regions of Russian Federation. 290 patients (mean age: 53 years; age range: 21–89 years) were recruited in the N.N. Petrov Institute of Oncology (St.-Petersburg), which provides the treatment to the residents of North-Western Russia. In addition, the study included 64 women with OC (mean age: 59 years; age range: 33–78 years) from the regional oncological hospital of the city of Krasnodar, which is located in Southern Russia, more than two thousands kilometers aside from the first spot of patients collection. Almost all patients had Slavic ethnic origin. DNA isolation, design of PCR assays and other relevant technical information is described in detail in our earlier report [42].

The observed frequencies of founder mutations are presented in the Table 1. BRCA1 5382insC mutation was by far the most prevalent, accounting for 28/290 (9.7%) OC cases from the North-West and 11/64 (17.2%) from the South of Russia. Jewish BRCA1 variant, BRCA1 185delAG, was the second by prevalence: it was detected in 3/290 (1.0%) cases from St.-Petersburg and in 1/64 (1.6%) patients from Krasnodar. BRCA1 4153delA mutation was revealed only in 2/290 (0.7%) subjects from the first cohort, and BRCA1 300T>G was not observed in any sample tested. When both patients groups were pooled together, the occurrence of founder BRCA1 mutations approached to 12.7% (45/354). Other breast cancer associated founder mutations (BRCA2, CHEK2, NBS1) were detected only in single patients. Interestingly, 1 OC patient from Krasnodar carried both BRCA1 5382insC and NBS1 657del5 mutation; tumor tissue from this woman demonstrated loss of heterozygosity of the wild-type NBS1 allele, but intact status of BRCA1 gene. This unique case is presented in detail in a separate publication [43]. Based on the results of DNA test and the history of cancer diseases in her family, this patient opted for prophylactic subcutaneous nipple-sparing mastectomy coupled with the immediate breast reconstruction by silicone...
implant; morphological examination of the excised mammary tissue revealed no evidence for the tumor growth.

Distribution of founder mutations in various OC subgroups is analyzed in Table 2. Patients from St.-Petersburg did not demonstrate association with early age at onset, while the mutation carriers were somewhat overrepresented in younger patients from Krasnodar (10/34 (29.4%) in patients aged <= 60 years versus 2/30 (6.7%) in older women; p = 0.02). Family history records were available only for the patients from the North-West; no association between the presence of the germ-line mutations and reporting OC or BC in a first-degree relative has been observed. Furthermore, there was no significant difference between carriers and non-carriers with respect to other clinico-pathological parameters of the disease.

**Discussion**

This study was designed to analyze the impact of selected founder mutations in OC morbidity in Russia. The panel of genetic variants included several alleles, which are characteristic for Slavic people and/or residents of Baltic regions (BRCA1 5382insC, BRCA1 4153delA, BRCA1 300T>G, CHEK2 1100delC, CHEK2 1100delC, CHEK2 1100delC, CHEK2 6174delT), and/or European Jews (BRCA1 185delAG, BRCA2 6174delT). This study confirmed the utmost role of BRCA1 5382insC mutation in cancer morbidity: indeed, this single genetic defect is responsible for as many as 1 out of 9 ovarian cancers and 1 out of 25 breast cancers occurring in Russia. Furthermore, BRCA1 5382insC demonstrates unique geographic spread, being among the most prevalent BRCA variants in Poland, Byelorussia, Baltic republics, various cities of Russian Federation (St.-Petersburg, Tomsk, and Krasnodar), and possibly some Mediterranean countries [42,44-49]. The remarkable role of the founder effect contradicts to the wide-spread view that the extreme complexity of the history of Russian Empire resulted in huge genetic diversity of Russian residents. It is important to emphasize, that recent investigations show surprisingly high level of genetic homogeneity for the 3 analyzed Slavic-speaking populations, i.e. Russians, Ukrainians and Poles [50]. These unexpected data are in good agreement with the lack of language diversity within the Russian Federation: astonishingly, people residing nearby Baltic sea or in the Far East speak exactly the same dialect, despite being separated by the distance of 1100 kilometers.

Other BRCA1 founder mutations are relatively rare in Russian ovarian or breast cancer cases [42]. BRCA1 4153delA allele was initially considered to be characteristic for familial OC in Russia [44]; furthermore, it was suggested that this variant confers specific predisposition to the ovarian but not breast carcinogenesis [25,48]. Our data do not confirm these statements. Jewish BRCA1 185delAG allele is occasionally detected in Russian OC and BC cases, while Baltic BRCA1 300T>G variant demonstrates null occurrence and therefore has to be excluded from the local diagnostic panel [42]. Taken together with other reports on OC patients or healthy controls [36-38,51], this study does not support the role of CHEK2 gene lesions in OC predisposition (Table 1). On the other hand, the possibility of limited contribution of NBS1 germ-line mutations in OC risk cannot be fully excluded. Previously, Plisiecka-

| Table 1: Founder mutations in Russian ovarian cancer cases |
|----------------------------------------------------------|
|                                                         |
| **St.-Petersburg (n = 290)**                             |
| BRCA1 5382insC                                           |
| 28 (9.7%)                                                |
| BRCA1 4153delA                                           |
| 2 (0.7%)                                                 |
| BRCA1 185delAG                                           |
| 3 (1.0%)                                                 |
| BRCA1 300T>G                                            |
| -                                                       |
| BRCA2 6174delT                                           |
| 1 (0.3%)                                                 |
| CHEK2 1100delC                                           |
| 2 (0.7%)                                                 |
| CHEK2 IVS2+1G>A                                         |
| -                                                       |
| NBS1 657del5                                            |
| -                                                       |
| **Total carriers**                                       |
| 36 (12.4%)                                               |

| **Krasnodar (n = 64)**                                   |
| BRCA1 5382insC                                           |
| 11 (17.2%)                                              |
| BRCA1 4153delA                                           |
| -                                                       |
| BRCA1 185delAG                                           |
| 1 (1.6%)                                                 |
| BRCA1 300T>G                                            |
| -                                                       |
| BRCA2 6174delT                                           |
| -                                                       |
| CHEK2 1100delC                                           |
| -                                                       |
| CHEK2 IVS2+1G>A                                         |
| -                                                       |
| NBS1 657del5                                            |
| 1 (1.6%)                                                 |
| **Total carriers**                                       |
| 12 (18.8%)                                              |

*1 patient from Krasnodar carried both BRCA1 5382insC and NBS1 657del5 mutations.
Table 2: Frequencies of founder mutations in distinct categories of ovarian cancer patients

| Clinical variable | St.-Petersburg (n = 290) | Krasnodar (n = 64) |
|-------------------|--------------------------|-------------------|
| Age at onset (years) |                          |                   |
| < 41              | 2/36 (5.6%)              | 1/1 (100.0%)      |
| 41–60             | 22/172 (12.8%)           | 9/33 (27.2%)      |
| > 60              | 12/82 (14.6%)            | 2/30 (6.7%)       |
| Non-informative   | -                        |                   |
| Family history*   |                          |                   |
| Positive          | 1/9 (11.1%)              | -                 |
| Negative          | 33/266 (12.4%)           | -                 |
| Non-informative   | 2/15 (13.3%)             | 12/64 (18.8%)     |
| T status          |                          |                   |
| T1                | 2/52 (3.8%)              | 3/10 (30.0%)      |
| T>1               | 32/220 (14.5%)           | 8/53 (15.1%)      |
| Non-informative   | 2/18 (11.1%)             | 1/1 (100.0%)      |
| N status          |                          |                   |
| N0                | 12/109 (11.0%)           | 1/4 (25.0%)       |
| N1                | 7/53 (13.2%)             | 1/1 (100.0%)      |
| N2                | 1/1 (100.0%)             | -                 |
| Non-informative   | 16/127 (12.6%)           | 10/59 (16.9%)     |
| M status          |                          |                   |
| M0                | 22/186 (11.8%)           | 11/58 (19.0%)     |
| M1                | 6/63 (9.5%)              | 0/4 (0.0%)        |
| Non-informative   | 8/41 (19.5%)             | 1/2 (50.0%)       |
| Tumor grade       |                          |                   |
| 1–2               | 7/96 (7.3%)              | 9/48 (18.8%)      |
| 3                 | 23/154 (14.9%)           | 3/16 (18.8%)      |
Halasa et al. [39] identified 2 NBS1 657del5 mutation carriers among 117 OC patients. In the present study, the frequency of NBS1 heterozygosity in OC patients (0.3%) did not differ significantly from the estimate obtained in healthy Russian women (0.6%) [52]. However, tumor tissue from the BRCA1/NBS1 heterozygous carrier from our OC group contained biallelic inactivation of NBS1 but not BRCA1 [43].

Most of the published investigations reported a correlation between the presence of BRCA1 mutation and family history of breast/ovarian cancer as well as earlier onset of the disease. Some reports also noticed association of BRCA1 heterozygosity with non-mucinous tumor histology, high tumor grade, and improved survival (see additional file 1). Nevertheless, almost all investigators agree that neither lack of family history nor late disease onset are reliable indicators of BRCA1 wild-type status in OC patients, therefore DNA testing of non-selected ovarian cancer cases is recommended by some laboratories. Our study failed to detect relationships between BRCA1 germline mutations and first-degree family history. There are some factors, which could complicate the analysis of pedigrees for BC and OC cases. First of all, BRCA1-related cancers are mainly gender-specific; i.e. male carriers of BRCA1 defects do not experience significantly elevated cancer risk due to absence of the main target organs (breasts and ovaries); therefore, family history negative BRCA1-associated BC and OC are particularly likely in case of paternal transmission of the mutation. Other confounding effects are related to specific circumstances of recent history of Russian Federation. Huge human losses caused by historical turbulences in the XX century, taken together with limited average life expectancy, led to the situation when many BRCA1 carriers simply failed to achieve the age of cancer manifestation due to premature death. Another factor, that may increase the number of false-negative pedigrees, is a relatively low number of children per family in the modern Russia; in other words, many of questioned patients could recall only a small number if any of their adult female relatives. Finally, an analysis of heredity is frequently ignored by Russian medical professionals, i.e. family history records in medical charts may simply lack a sufficient level of accuracy.

**Conclusion**

This study indicates that all ovarian cancer patients of Russian ethnic origin have to be screened for the presence of a few BRCA1 founder mutations (BRCA1 5382insC, BRCA1 185delAG, BRCA1 4153delA). Introduction of this cheap DNA test into routine medical practice may help to identify yet healthy relatives of OC patients, who carry the same genetic defect and thus will benefit from tight surveillance and/or prophylactic surgery. Furthermore, recent findings suggest that BRCA1-associated ovarian cancers may require distinct strategy for the disease treatment [53].

**Abbreviations**

BC: breast cancer; OC: ovarian cancer

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

ENS, APS, AGI, AVT, SYM, AFU, NVP and ENI contributed in the conception of the study. NYS, DNP, TVG, OAZ, OSY, AVT, NNT, GAS, OSL, NYK, DEM, SYM, AFU were responsible for data collection. ENS, APS, NVP, ENI performed data analysis. ENI wrote the manuscript. All authors approved the final version.
Additional material

Additional file 1
Germ-line mutations in non-selected ovarian cancer patients. Table-format summary of the literature data on BRCA1, BRCA2, CHEK2, and NBS1 germ-line mutations in non-selected ovarian cancer patients
Click here for file
[http://www.biomedcentral.com/content-supplementary/1897-4287-7-51.s1]

Acknowledgements
This work is supported by INTAS (grant 05-1000008-7870), Grant for Helmholtz-Russia Joint Research Groups (grant HRJRG-006/07-04-9282-à), Russian Foundation for Basic Research (grants 07-04-00122-à, 07-04-00172-à, 08-04-00369-à), and the Russian Academy of Sciences (grant “Molecular and Cell Biology”). We cordially thank Prof. Peter Devilee (Leiden University Medical Center, The Netherlands) for the fruitful discussion.

References
1. DeVita VT Jr, Hellman S, Rosenberg SA, Eds: “Cancer: principles and practice in oncology eighth edition. Lippincott Williams and Wilkins; 2008.
2. Abeliovich D, Kaduri L, Lerer I, Weinberg N, Amir G, Sagi M, Zlotogora J, Heching N, Perez T: The founder mutations 185delAG and 5182insC in BRCA1 and 6174delT in BRCA2 appear in 60% of ovarian cancer and 30% of early-onset breast cancer patients among Ashkenazi women. Am J Hum Genet 1997, 60:505-514.
3. Beller U, Halle D, Catane R, Kaufman B, Hornreich G, Levy-Lahad E: High frequency of BRCA1 and BRCA2 germline mutations in Ashkenazi Jewish ovarian cancer patients, regardless of family history. Gynecol Oncol 1997, 67:123-126.
4. Tobias DH, Eng C, McCurdy LD, Kalir T, Mandelli J, Dottino PR, Ramus SJ, Fishman A, Pharoah PD, Yarkoni S, Altaras M, Ponder BA: High frequency of BRCA1 and BRCA2 mutations among ovarian cancer patients in Israel. Gynecol Oncol 2003, 89:3-15.
5. Beller U, Halle D, Catane R, Kaufman B, Hornreich G, Levy-Lahad E: High frequency of BRCA1 and BRCA2 germline mutations in Ashkenazi Jewish ovarian cancer patients, regardless of family history. Gynecol Oncol 1997, 67:123-126.
6. Ramus SJ, Fishman A, Pharoah PD, Yarkoni S, Altaras M, Ponder BA: Ovarian cancer survival in Ashkenazi Jewish patients with BRCA1 and BRCA2 mutations. Eur J Surg Oncol 2001, 27:278-281.
7. Contri CR, Matesic M, Svecic M, Naumovic D, Tomic S, Boljevic I, Kuzmanovic N: Four BRCA1 and BRCA2 mutations are identified in two consecutive ovarian cancer patients. J Med Genet 2000, 37:142-145.
8. Beller U, Halle D, Catane R, Kaufman B, Hornreich G, Levy-Lahad E: High frequency of BRCA1 and BRCA2 germline mutations in Ashkenazi Jewish ovarian cancer patients, regardless of family history. Gynecol Oncol 1997, 67:123-126.
9. Tobias DH, Eng C, McCurdy LD, Kalir T, Mandelli J, Dottino PR, Ramus SJ, Fishman A, Pharoah PD, Yarkoni S, Altaras M, Ponder BA: High frequency of BRCA1 and BRCA2 mutations among ovarian cancer patients in Israel. Gynecol Oncol 2003, 89:3-15.
10. Beller U, Halle D, Catane R, Kaufman B, Hornreich G, Levy-Lahad E: High frequency of BRCA1 and BRCA2 germline mutations in Ashkenazi Jewish ovarian cancer patients, regardless of family history. Gynecol Oncol 1997, 67:123-126.
11. Ramus SJ, Fishman A, Pharoah PD, Yarkoni S, Altaras M, Ponder BA: Ovarian cancer survival in Ashkenazi Jewish patients with BRCA1 and BRCA2 mutations. Eur J Surg Oncol 2001, 27:278-281.
12. Cass I, Baldwin RL, Varkey T, Moslehi R, Narod SA, Karlan BY: Improved survival in women with BRCA-Associated ovarian carcinoma. Cancer 2003, 97:2187-2195.
13. Tobias DH, Eng C, McCurdy LD, Kalir T, Mandelli J, Dottino PR, Cohen CJ: Founder BRCA1 and 2 mutations among a consecutive series of Ashkenazi Jewish ovarian cancer patients. Gynecol Oncol 2000, 78:148-151.
14. Boyd J, Sonoda Y, Federici MG, Bogomolny F, Rhei E, Mascolo DL, Saigo PE, Almadrones LA, Barakat RR, Brown CL, Chi DS, Curtin JP, Poynor EA, Hoskins WJ: Clinicopathologic features of BRCA1-linked and sporadic ovarian cancer. JAMA 2000, 283:2260-2265.
15. Satagopan JM, Boyd J, Kauf ND, Robson M, Scheuer L, Narod S, Offit K: Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. Clin Cancer Res 2004, 10:3776-3781.
16. Moslehi R, Chu W, Karlan B, Fishman D, Risch H, Fields A, Smoktin D, Ben-David Y, Rosenblatt J, Russo D, Schwartz P, Tung N, Warner E, Rosen B, Friedman J, Brunet JS, Narod SA: BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer. Am J Hum Genet 2000, 66:1239-1272.
17. Tong D, Stampf M, Reinehaller A, Vavra N, Mullauer-Ertl S, Leodolter S, Zellinger R: BRCA1 gene mutations in sporadic ovarian carcinomas: detection by PCR and reverse allele-specific oligonucleotide hybridization. Clin Chem 1999, 45:976-982.
18. Trott PN, Mask-Masson AM, Narod SA, Ghadirian P, Provencek D: Founder BRCA1 and BRCA2 mutations in French Canadian ovarian cancer cases unselected for family history. Clin Genet 1999, 55:318-324.
19. Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Kwan E, Jack E, Vespriini DJ, Kuperstein G, Abrahamson JL, Fan I, Wong B, Narod SA: Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. Am J Hum Genet 2001, 68:700-710.
20. Sarantaus L, Vahteristo P, Bloom E, Tamminen A, Unkila-Kallio L, Butzow R, Nevanlinna H: BRCA1 and BRCA2 mutations among 233 unselected Finnish ovarian carcinoma patients. Eur J Hum Genet 2001, 9:424-430.
21. Fooj M, Van Der, Sabo C, Besznyak I, Liszka G, Csookay B, Pulay T, Toth J, Devilee P, King MC, Olah E: Prevalence of founder BRCA1 and BRCA2 mutations among breast and ovarian cancer patients in Hungary. Int J Cancer 2000, 86:737-740.
22. Johannesdotir G, Gudmundsson J, Berghorston JT, Arason A, Agnarsson BA, Eiriksdottir G, Johannsson OT, Borg A, Ingvarsson S, Easton DF, Egilsson V, Barkardott RB: High prevalence of the 999del5 mutation in Icelandic breast and ovarian cancer population. Cancer Res 1999, 59:4308-4310.
23. Hirsh-Yechezkel G, Chetrit A, Lubin F, Friedman E, Peretz T, Gershoni R, Rizel S, Struweing JP, Modan B: Population attributes affecting the prevalence of BRCA mutation carriers in epithelial ovarian cancer cases in Israel. Gynecol Oncol 2003, 89:494-498.
24. Ben David Y, Chetrit A, Hirsh-Yechezkel G, Friedman E, Beck BD, Beller U, Ben-Baruch G, Fishman A, Levavi H, Lubin F, Menzner J, Piura S, Struweing JP, Modan B, National Israeli Study of Ovarian Cancer: Effect of BRCA mutations on the length of survival in epithelial ovarian tumors. J Clin Oncol 2002, 20:463-466.
25. Chetrit A, Hirsh-Yechezkel G, Ben-David Y, Lubin F, Friedman E, Sadetzki S: Effect of BRCA1/2 mutations on the long-term survival of patients with invasive ovarian cancer: the national Israeli study of ovarian cancer. J Clin Oncol 2008, 26:20-25.
26. Matushima M, Kobayashi K, Emi M, Saito H, Saito J, Suzumori K, Nakamura Y: Mutation analysis of the BRCA1 gene in 76 Japanese ovarian cancer patients: four germline mutations, but no evidence of somatic mutation. Hum Mol Genet 1995, 4:1953-1956.
27. Kim YN, Tan EM, Yoon BS, Kim SM, Kim SH, Kim HK, Koo JS, Kim JW: Germline mutations of BRCA1 and BRCA2 in Korean sporadic ovarian carcinoma. Gynecol Oncol 2005, 99:585-590.
28. Darum A, Hovig E, Tropc C, Inganas M, Moller P: Three per cent of Norwegian ovarian cancers are caused by BRCA1 1675delA or 1135insA. Eur J Cancer 1999, 35:779-781.
29. Jacobi CE, van Ierland Y, van Asperen CJ, Hallensleben E, Devilee P, Jan Fleuron G, Kenter GG: Prediction of BRCA1/2 mutation status in patients with ovarian cancer from a hospital-based cohort. Genet Med 2007, 9:173-179.
30. Looij M van Der, Szabo C, Besznyak I, Liszka G, Pulay T, Toth J, Devilee P, King MC, Olah E: Prevalence of the 999del5 mutation in BRCA1 and BRCA2 mutations among 233 unselected Finnish ovarian carcinoma patients. Eur J Hum Genet 2001, 9:424-430.
31. Easton DF, Egilsson V, Agnarsonn BA: The prevalence of BRCA1 and BRCA2 mutations among breast and ovarian cancer patients in Turkey. Int J Cancer 1999, 83:5 http://www.hccpjournal.com/content/7/1/5.
30. Takahashi H, Chiu HC, Bandera CA, Behbakht K, Liu PC, Couoch FJ, Weber BL, LiVolsi VA, Furusato M, Rebane BA, Cardonick A, Benjamin I, Morgan MA, King SA, Mikuta J.J, Rubin SC, Boyd J: Mutations of the BRCA2 gene in ovarian carcinomas. Cancer Res 1995, 55:2738-2741.

31. Takahashi H, Behbakht K, McGovern PE, Chiu HC, Couoch FJ, Weber BL, Friedman LS, King MC, Furusato M, LiVolsi VA, Menzlin AW, Liu PC, Benjamin I, Morgan MA, King SA, Rebane BA, Cardonick A, Mikuta J.J, Rubin SC, Boyd J: Mutation analysis of the BRCA1 and BRCA2 genes in ovarian carcinomas. Cancer Res 1995, 55:2998-3002.

32. Rubin SC, Blackwood MA, Bandera C, Behbakht K, Benjamin I, Rebeck TR, Boyd J: BRCA1, BRCA2, and hereditary nonpolyposis colorectal cancer gene mutations in an unselected ovarian cancer population: relationship to family history and implications for genetic testing. Am J Obstet Gynecol 1998, 178:670-677.

33. Anton-Culver H, Cohen PF, Gioldas A: Characteristics of BRCA1 mutations in a population-based case series of breast and ovarian cancer. Eur J Cancer 2000, 36:1200-1208.

34. Smith SA, Richards WE, Caikeo K, Hanjani P, Markman M, DeGeest K, Gallon HH: BRCA1 germline mutations and polymorphisms in a clinic-based series of ovarian cancer cases: a Gynecologic Oncology Group study. Gynecol Oncol 2001, 83:S586-592.

35. Pat J, Perriman A, Bets J, Krücher JP, Fiorica J, Arango H, LaPolla J, Hoffman M, Martino MA, Wakeley K, Wilbanks G, Niccota S, Cantor A, Sutphen R: BRCA1 and BRCA2 mutations account for a large proportion of ovarian cancer cases. Cancer 2005, 104:2807-2816.

36. Smyrnaios-Pasternak J, Smyrnaios A, Medrek K, Imyanitov EN, Cybulski C, Gorski B, Magnowski P, Dzuba I, Gugala K, Debnik B, Gozdzi S, Sokolenko AP, Krylova NY, Lobeiko OS, Narod SA, Lubinski J: CHEK2 variants predispose to benign, borderline and low-grade invasive ovarian tumours. Gynecol Oncol 2006, 102:429-431.

37. Byrski T, Deloia JA, Willett-Brozick JE, Goodman MT, Brady MF, Modugno F, Lynch HT, Conley YP, Watson P, Gallion HH: Analysis of CHEK2 gene variants for ovarian cancer susceptibility. Gynecol Oncol 2004, 95:62-69.

38. Williams LH, Choong D, Johnson SA, Campbell IG: Genetic and epigenetic analysis of CHEK2 in sporadic breast, colon, and ovarian cancers. Clin Cancer Res 2006, 12:6967-6972.

39. Plisiacka-Halasa J, Dansonka-Miszewska A, Rembiszewska A, Bzdziatski M, Steffen J, Kupryjaścicyk J: Nijmegen breakage syndrome gene (NBS1) alterations and its protein (nibrin) expression in human tumour tissues. Ann Hum Genet 2002, 66:353-359.

40. Steffen J, Varon R, Mosor M, Maneva G, Pflauher M, Stumm M, Nowakowska D, Rubach M, Kosakowska E, Ruza W, Nowacki Z, Rutkowski P, Demko T, Sadowska M, Bzdziatski M, Gozdz S, Sokolenko AP, Krylova NY, Lobeiko OS, Narod SA, Lubinski J: NBS1 germline mutations in Poland. Int J Cancer 2005, 115:677-681.

41. Paczkowski JA, Olopade OI: Breast cancer risk associated with BRCA1 and BRCA2 in diverse populations. Nat Rev Cancer 2007, 7:937-948.

42. Sokolenko AP, Rozanov ME, Mitsushkina NV, Sherina NY, Iyevleva AG, Chekmariova EV, Buslov KG, Shilov ES, Togo AV, Matsko DE, Semiglazov VF, Deivele P, Cornelisse C, Semiglazov VF, Imyanitov EN: CHEK2 1100delC mutation is frequent among Russian breast cancer patients. Breast Cancer Res Treat 2006, 100:99-102.

43. Buslov KG, Iyevleva AG, Chekmariova EV, Susuptsin EN, Togo AV, Kuligina ES, Sokolenko AP, Platsko DE, Turkheev IA, Lazareva YR, Chagunova OL, Bit-Sava EM, Semiglazov VF, Deivele P, Cornelisse C, Hansson KP, Imyanitov EN: NBS1 657del5 mutation may contribute only to a limited fraction of breast cancer cases in Russia. Int J Cancer 2005, 114:585-589.

44. Kauff ND: Is it time to stratify for BRCA mutation status in therapeutic trials in ovarian cancer? J Clin Oncol 2008, 26:9-10.

45. Tereschenko IV, Basham VM, Ponder BA, Pharoah PD: BRCA1 and BRCA2 mutations in Russian familial breast cancer. Hum Mutat 2002, 19:184.

46. Górska B, Cybulski C, Huzarski T, Byrski T, Gronwald J, Jakubowska A, Stawicka M, Gozdecka-Grocdecka S, Szwiez M, Urbański K, Mitrjuk Z, Marzyk E, Dzuba J, Wendzel P, Sudyka D, Haus O, Janiszewska H, Debnik T, Tołoczko-Grabarek A, Medrek K, Masióe B, Mierzewjski M, Kowalska E, Narod SA, Lubinski J: Breast cancer predisposing alleles in Poland. Breast Cancer Res Treat 2005, 92:19-24.

47. Tikhomirova L, Sinicka O, Smite D, Eglitis J, Hodgson SV, Stangreics A: High prevalence of two BRCA1 mutations, 4154delA and 5382insC, in Latvia. Fam Cancer 2005, 4:77-84.

48. Balanovskiy O, Rootsi S, Pshenichnov A, Kivisild T, Churnosov M, Esvese A, Pocheshkhlava E, Boldyrev M, Yankovsky N, Balanovskiy E, Vilemis R: Two sources of the Russian patrilineal heritage in their Eurasian context. Am J Hum Genet 2008, 82:236-250.

49. Chekmariova EV, Sokolenko AP, Buslov KG, Iyevleva AG, Ulibina YM, Rozanov ME, Mitsushkina NV, Togo AV, Matsko DE, Voskresenskiy DA, Chagunova OL, Deivele P, Cornelisse C, Semiglazov VF, Imyanitov EN: CHEK2 1100delC mutation is frequent among Russian breast cancer patients. Breast Cancer Res Treat 2006, 100:99-102.

50. Buslov KG, Iyevleva AG, Chekmariova EV, Susuptsin EN, Togo AV, Kuligina ES, Sokolenko AP, Platsko DE, Turkheev IA, Lazareva YR, Chagunova OL, Bit-Sava EM, Semiglazov VF, Deivele P, Cornelisse C, Hansson KP, Imyanitov EN: NBS1 657del5 mutation may contribute only to a limited fraction of breast cancer cases in Russia. Int J Cancer 2005, 114:585-589.

51. Kauff ND: Is it time to stratify for BRCA mutation status in therapeutic trials in ovarian cancer? J Clin Oncol 2008, 26:9-10.

Publish with BioMed Central and every scientist can read your work for free of charge

"BioMed Central will be the most significant development for disseminating the results of biomedical research in our lifetime." Sir Paul Nurse, Cancer Research UK

Your research papers will be:
- available free of charge to the entire biomedical community
- peer reviewed and published immediately upon acceptance
- cited in PubMed and archived on PubMed Central
- yours — you keep the copyright

Submit your manuscript here:
http://www.biomedcentral.com/info/publishing_adv.asp