Hereditary Cancer in Clinical Practice 2008; 6(2) pp. 88-98

Hereditary breast and ovarian cancer

Jacek Gronwald[1], Tomasz Byrski[1], Tomasz Huzarski[1], Oleg Oszurek[1], Anna Janicka[1], Jolanta Szymańska-Pasternak[1], Bohdan Górski[1], Janusz Menkiszak[2], Izabella Rzepka-Górska[2], Jan Lubiński[1]

[1]International Hereditary Cancer Centre, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland
[2]Pomeranian Medical University, Department of Surgical Gynaecology and Gynaecological Oncology of Adults and Adolescents, Szczecin, Poland

Corresponding author: Jacek Gronwald, International Hereditary Cancer Centre, Department of Genetics and Pathology, Pomeranian Medical University, Połabska 4, 70-115 Szczecin, Poland, e-mail: jgron@sci.pam.szczecin.pl

Familial breast cancer was first recognized in the Roman medical literature of 100 AD [1]. The first documentation of familial clustering of breast cancer in modern times was published by Broca, who reported 10 cases of breast cancer in 4 generations of his wife's family [2]. In the middle of the nineteen nineties it was proven at the molecular level that a substantial number of breast and ovarian cancers has hereditary monogenic aetiology [3, 4]. Evaluation of frequency of pedigree-clinical signs characteristic for strong aggregations of breast/ovarian cancers among consecutive cases of cancers of these organs as well as analyses of cancer incidence in monozygotic twins indicate that about 30% of breast and ovarian cancers develop because of a strong genetic predisposition [5]. In other breast/ovarian cancers the significance of genetic factors was underestimated. However, recently it has been possible to show the characteristic constitutional background influencing development of cancer also in patients with sporadic neoplasms. Therefore now scientists think that in almost all patients with cancer a certain genetic background should be detectable, although influencing cancer risk to a various degree. Genetic abnormalities strongly related to cancer are called high risk changes (genes) and abnormalities influencing cancer development to a lower degree are called moderate risk changes (genes). Most frequently strong genetic predisposition to breast/ovarian cancers are related to mutations in the *BRCA1* and *BRCA2* genes and most often it appears as syndromes of hereditary breast cancer – site-specific (HBC-ss), hereditary breast-ovarian cancer (HBOC) and hereditary ovarian cancer (HOC).

In family members of families with HBC-ss syndrome only breast cancers but not ovarian cancers are observed. In HBOC syndrome families both breast and ovarian cancers are diagnosed, and in HOC syndrome only ovarian but not breast cancers are detected. Operational clinical-pedigree criteria which we use in order to diagnose "definitively" or "with high probability" the discussed syndromes are summarized in Table 1. In the vast majority of cancer cases related to moderate risk genes family history is negative. HBC-ss, HBOC and HOC syndromes are clinically and molecularly heterogeneous. Mutations in the *BRCA1* and *BRCA2* genes are the most frequent cause of these syndromes.

Table 1. Pedigree-clinical diagnostic criteria of HBC-ss, HBOC and HOC syndromes [6]

Number of breast or ovarian cancer cases in family:
A – 3 (definitive diagnosis)
1) At least 3 relatives affected with breast or ovarian cancer diagnosed at any age
B – 2 (highly probable diagnosis)
1) 2 breast or ovarian cancer cases among first degree relatives (or second degree through male line)
2) 1 breast cancer and 1 ovarian cancer diagnosed at any age among first degree relatives (or second degree through male line)
C – 1 (highly probable diagnosis)
1) Breast cancer diagnosed below 40 years of age
2) Bilateral breast cancer
3) Medullary or atypical medullary breast cancer
4) Breast and ovarian cancer in the same person
5) Breast cancer in male

BRCA1 syndrome

In this syndrome women carry a germline mutation in the *BRCA1* gene. Carriers of a *BRCA1* mutation have approximately 50-80% lifetime risk of breast cancer and 40% risk of ovarian cancer [7]. We estimate that these risks are 66% for breast cancer and 44% for ovarian

Table 2. Risk of breast and ovarian cancer in *BRCA1* mutation carriers in Poland [8]

A. Cumulated risk of breast cancer						
Age	<30	40	50	60	70	75
Cumulated risk (%)	1.6	6.5	30	40.5	50.5	66
B. Cumulated risk of ovarian cancer						
Age	<30	40	50	60	70	75
Cumulated risk (%)	1	3.5	12	30	41	44

cancer in the Polish population (Table 2). Both risks appear to be dependent on the type and localization of the mutation [8-10]. Our findings suggest that the risk of breast cancer in women with 5382insC is two times higher than in women with 4153delA.

Incomplete penetrance of *BRCA1* suggests that other factors, genetic and non-genetic modifiers, are important in carcinogenesis in the mutation carriers. The risk of ovarian cancer is modified by VNTR *locus* for HRAS 1 and is increased 2-fold in *BRCA1* carriers harbouring one or two rare alleles of HRAS 1 [11]. We reported that the 135G>C variant in the *RAD51* gene is strongly protective (OR =0.5) against both ovarian and breast cancer [12,13].

Carriers of a *BRCA1* mutation are also at about 10% lifetime risk of fallopian tube and peritoneal cancers [14]. These data about the frequency of ovarian cancer in *BRCA1* carriers appear to reflect the combined frequency of ovarian, fallopian tube and peritoneal cancers, because these tumours were diagnosed as ovarian cancers in the past, and because they share similar morphology and cause elevated levels of the marker CA 125.

The risk of cancer at other sites may be increased in carriers of a *BRCA1* mutation as well, but the evidence is controversial and needs further studies.

Breast and ovarian cancer in *BRCA1* carriers have particular clinical characteristics. The mean age at onset of breast cancer is about 42-45 years [15, 16] and of ovarian cancer is about 54 years [17, 18]. 18-32% of breast cancers are bilateral [19, 20]. These are rapidly growing tumours: >90% of cases have G3 grade at the time of diagnosis and almost all ovarian cancers in women with a *BRCA1* mutation are diagnosed in FIGO stage III°/IV°. Medullary, atypical medullary, ducal and oestrogen receptor negative (ER) breast tumours are common in *BRCA1* carriers. *BRCA1* mutation-positive tumours constitute about 10-15% of all ER-breast cancers [21-23]. Most carriers of a *BRCA1* mutation report a positive family history of breast or ovarian cancer (Figure 1). However, 45% of *BRCA1*

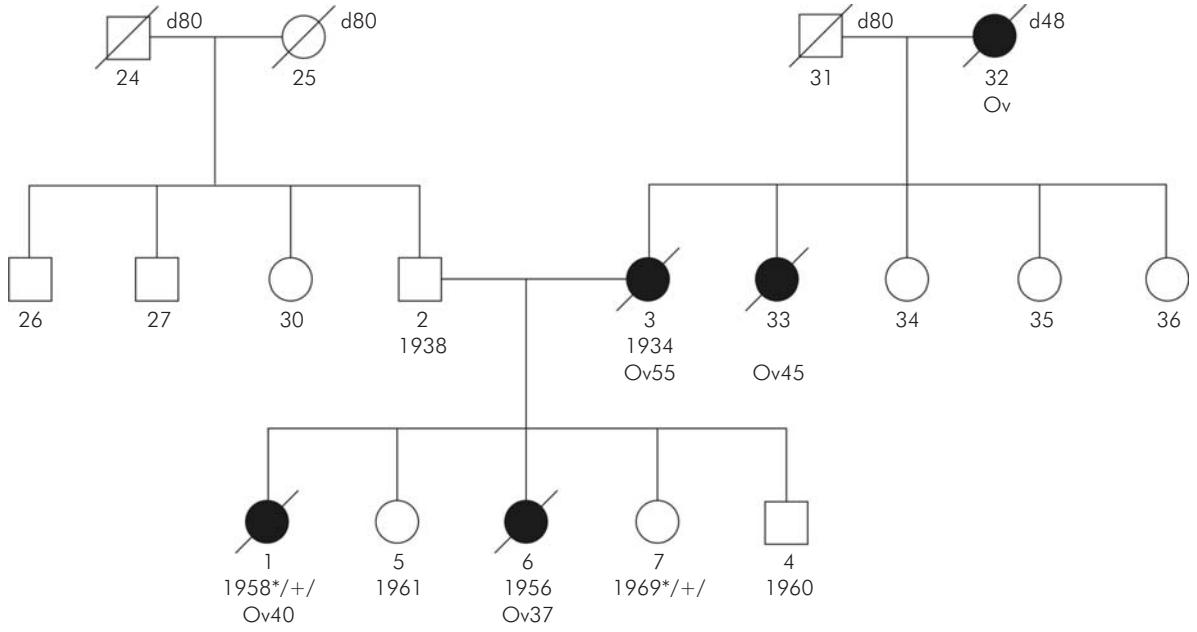

Figure 1. Family with HOC syndrome and diagnosed constitutional 4153delA *BRCA1* gene mutation

carriers report a negative family history, mainly because of paternal inheritance and incomplete penetrance (Figure 3) [20].

Molecular diagnosis of constitutional *BRCA1* mutations

This topic has been described in detail in the section "*BRCA1* Test".

BRCA2 syndrome

Patients with this syndrome have a constitutional mutation in the *BRCA2* gene [24]. According to literature data lifetime risk for *BRCA2* carriers from families with definitive HBC-ss and HBOC is estimated at 31-56% for breast cancer and 11-27% for ovarian cancer [10, 25-28]. Studies performed in 200 Polish families with strong aggregation of breast and/or ovarian cancers proved that mutations in the *BRCA2* gene are rare, with a frequency of 4%. There are no studies on cumulated cancer risk in *BRCA2* mutation carriers from the Polish population. Most *BRCA2* mutations from the Polish population probably slightly increase breast cancer risk. Studies performed in our centre showed that in families with aggregation of breast cancer diagnosed before the age of 50 and stomach cancer diagnosed in males before the age of 55, frequency of *BRCA2* carriers is about 10-20% [29]. *BRCA2* mutations are also related to a significantly increased although not precisely estimated risk of ovarian cancer and cancers of the digestive tract such as stomach, colon and pancreas in both females and males. Studies performed in our centre showed that

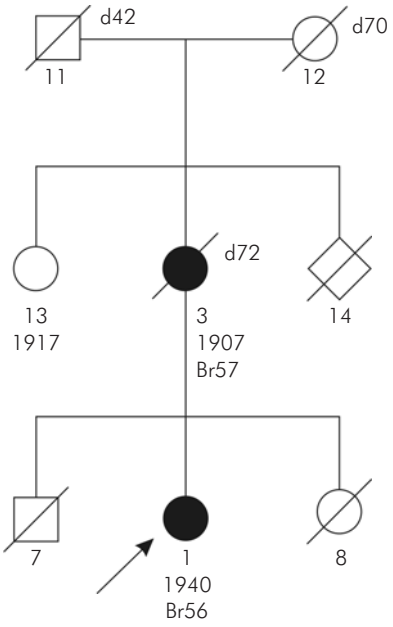

Figure 2. Family with fulfilled clinical-pedigree criteria "suspected HBC-ss". *BRCA1* mutation was not detected

BRCA2 mutations are detected with a frequency of 30% in families without breast cancer but with aggregation of ovarian cancer with stomach, colon or pancreatic cancer between first and second degree relatives [30]. *BRCA2* studies performed on male breast cancer patients from the Poznań population showed that 15% of patients from this group are mutation carriers [31].

Breast and ovarian cancers in families with *BRCA2* mutations have characteristic features. Medium age of breast cancer is 52 and 53 in females and males, respectively, and 62 for ovarian cancer [31, 32].

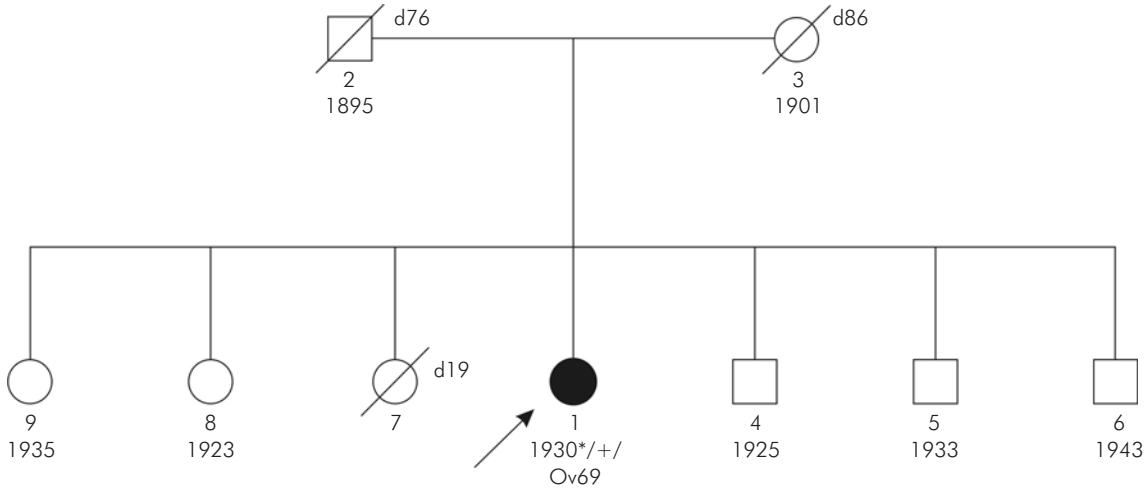

Figure 3. Patient with ovarian cancer and detected 5382insC *BRCA1* mutation from family with negative family history

Molecular diagnosis of *BRCA2* mutations

Unlike for the *BRCA1* gene, a founder effect for *BRCA2* mutations was not observed with significant frequency in the Polish population [22]. It should be noted that "de novo" mutations are rare in these groups of genes; thus the presence of founder mutations in *BRCA2* is probable. As yet *BRCA2* mutations should be diagnosed individually for each family by full sequencing. Since the *BRCA2* gene is large – about 70 genomic kbp – the cost of sequencing of this gene is high (around 1500 euro).

In families with a detected marker of constitutional mutation the cost of analysis of two independently taken blood samples allowing exclusion or confirmation of carrier status among relatives is low – around 100 euro.

BRCAX syndrome

In Poland in about 30% of families with definitively diagnosed HBC-ss and HBOC syndromes and in about 40% of families with HOC syndrome, *BRCA1* or *BRCA2* mutations are not detected. In rare cases it is possible to diagnose one of the rare syndromes listed in Table 3. In these syndromes breast/ovarian cancers are observed with higher frequency. Many groups worldwide are trying to identify new genes causing BRCAX syndrome.

Clinical management in families with high risk of breast/ovarian cancer

Special management should be applied for:

- carriers of mutations of high breast/ovarian cancer

Table 3. Selected rare syndromes with increased risk of breast and/or ovarian cancer

Disease	Clinical features	Gene mutation/ Inheritance	References
Li-Fraumeni syndrome	breast cancers, sarcomas, brain tumours, leukaemia, renal gland cancer	p53, high penetrance, AD	17, 33
Cowden disease	multifocal mucoid skin abnormalities, benign proliferative abnormalities of different organs, thyroid cancers, breast/ovarian cancers	PTEN, AD	34, 35
HNPCC	colon cancers, endometrial cancers, other organ cancers including breast and ovary	*MSH2, MLH1,* AD	36
Peutz-Jeghers syndrome	hyperpigmentation of the mouth, bowel polyps, colorectal cancers, small bowel cancers, gonadal tumours, breast cancers	STK11, AD	37
Ruvalcaba-Myhre-Smith (Z. Bannayan-Riley-Ruvalcaba) syndrome	macrocephaly, bowel polyps, "café-au-lait" on penis, lymphomas, thyroid cancers, breast cancers	PTEN, AD	38
Heterozygotic carrier status of "ataxia telangiectasia" gene	ocular ataxia, ataxia of cerebellum and skin, hypersensitivity to radiation, different site neoplasm including breast/ovarian cancer	ATM	39
ATH gene carriers	increased breast cancer risk	low penetrance 20-40%, AD	6
Klinefelter syndrome	gynaecomastia, cryptorchidism, extragonadal germ cell tumours, male breast cancer	47, XXY, low penetrance, <10%	40
Androgen receptor gene mutation	familial male breast cancer	androgen receptor	41
Constitutional translocation t(11q;22q)	increased breast cancer risk	balanced translocation t(11q;22q)	42

Inheritance
AD – autosomal dominant, AR – autosomal recessive

risk; usually around 50% of female family members should be included in the programme;
- all family members of families with HBC-ss, HBOC or HOC diagnosed definitively or with high probability according to pedigree criteria shown in Table 1, if constitutional mutations predisposing to cancer were not detected.

Special management concerns:
- prophylactics,
- surveillance,
- treatment.

Prophylactics

Oral contraceptives

Contraindications for use of oral contraceptives (OC) by *BRCA1* carriers aged below 25 are well documented. It was shown that OC used for 5 years by young women increase breast cancer risk by about 35% [43]. Since in about 50% of *BRCA1* carriers family history is negative it seems to be necessary to perform the *BRCA1* test in every young woman who wishes to use OC. OC used by *BRCA1* carriers after the age of 30 seems not to influence breast cancer risk [43-45] but shows a 50% reduction of ovarian cancer risk [34], so use of OC after the age of 30 appears to be justified. As yet, there are no verified data concerning the effects of OC in families not related to *BRCA1* mutation. However, there are studies indicating several-fold increased breast cancer risk in OC users from families with breast cancer aggregation [46]; thus it seams reasonable to avoid OC in families with HBC-ss and/or HBOC.

Hormone replacement therapy (HRT)

Prophylactic oopherectomy at the age of 35-40 is the gold standard for *BRCA1/2* carriers and corresponds with risk reduction for both breast and ovarian cancer. It was shown that carriers after oopherectomy, who use oestrogen HRT, show a similar protective effect as patients who do not use HRT [47, 48]. The influence of HRT in carriers without prophylactic oopherectomy is not well documented. Three-fold increased risk of breast cancer in HRT users with positive breast cancer family history was reported [49]. Therefore, the decision about HRT use should be made with particular caution.

Breast feeding

Long-term breast feeding is indicated in all females from families with HBC-ss, HBOC and HOC. It was shown in BRCA1 carriers that breast feeding over 18 months, counting together all pregnancies, reduces breast cancer risk – from 50-80% to 25-40% [50, 51].

Early delivery

Women from the general population who delivered the first child before the age of 20 are at 50% lower breast cancer risk than nulliparous women. This observation was not confirmed in women with *BRCA1* or *BRCA2* mutation [52]. However, taking into consideration the fact that mutation carriers should elect prophylactic oopherectomy at age 35-40, they should not delay maternity significantly.

Chemoprevention

Tamoxifen

Literature data clearly indicate that tamoxifen reduces by about 50% the risk of ER+ breast cancers. This effect was observed in healthy women as well as in women treated for breast cancer, where tamoxifen reduced the risk of contralateral breast cancer. A protective effect of tamoxifen was also observed in *BRCA1* carriers in spite of the fact that most cancers in these patients are ER-. Such an effect of tamoxifen was observed in pre- and postmenopausal women [53, 54]. According to present data it is justified to propose 5 year chemoprevention with tamoxifen to patients from families with HBC-ss, HBOC and *BRCA1* mutation carriers as well after exclusion of all contraindications, especially related to clotting problems and endometrial hypertrophy.

Selenium

Studies performed in our centre showed increased mutagen sensitivity in *BRCA1* carriers as measured with the bleomycin test. This sensitivity may be normalized with some selenium supplements [55]. Chemoprevention with selenium has been observed to reduce cancer risk in both humans and animals. This question should be answered in *BRCA1* carriers.

Adnexectomy

Both retrospective and prospective observations of patients with *BRCA1/2* mutations indicate that prophylactic adnexectomy decreases the risk of ovarian/peritoneal cancer to about 5% and breast cancer to 30-40%. Application of adnexectomy together with tamoxifen reduces breast cancer risk to about 10% in *BRCA1* carriers [14]. Therefore, in our centre adnexectomy is recommended to all *BRCA1/2* carriers aged over 35. This surgery is proposed to women from families with HBC-ss, HBOC and HOC but without detected *BRCA1/BRCA2* mutation only if other pathologies of the female genital tract were recorded during control examinations. About 85% of our patients accept this type of prophylaxis [56].

Mastectomy

The main target of prophylactic mastectomy is reduction of breast cancer risk by removal of tissue at risk. Single cases of breast cancer can develop from the chest wall or from the axillary cave after prophylactic mastectomy. It was noted, however, that only 1% of patients from this group develop breast cancer after prophylactic surgery [57]. It seams reasonable to offer this type of surgery to highly motivated patients with definitively diagnosed high cancer risk, especially where tumoural and mammographically dense breast glands are observed which make early diagnosis extremely difficult. At present, mastectomies with immediate reconstruction are performed most frequently. This procedure ensures a good cosmetic effect [58].

Surveillance

Surveillance in patients with HBC-ss, HBOC, HOC, as well as in *BRCA1/BRCA2* carriers is shown in Table 4. This scheme is individualized for particular patients with respect to age when particular examinations should begin. In some families where breast cancer was diagnosed before the age of 25 or ovarian cancer before the age of 35 surveillance should begin 5 years earlier than the age of diagnosis of cancer in this family. In some cases, in addition to breast and ovary investigations patients receive colonoscopy, gastroscopy or evaluation of PSA level and prostate ultrasound if in family members symptoms from the colon, gastric or urinal tract are observed. However, it should be noted that some control examinations have limited value in detection of early cancers in *BRCA1* carriers. Ovarian cancer in clinical stage I is detected in only 10% of women with a *BRCA1* mutation. On the other hand, magnetic resonance imaging in diagnosis of early breast cancers is introducing significant progress [28, 59]. This examination allows detection of 77% of breast cancers with diameter smaller than 1 cm and in combination with ultrasound its sensitivity in detection of early breast cancers rises to over 90% in *BRCA1* carriers [59].

Treatment

Existing data indicate that different rules should be applied or at least considered as an option in treatment of *BRCA1* carriers. They include:

- radical mastectomy instead of lumpectomy followed by radiation therapy, because the risk of local recurrence in the above procedures is 1% and 8%, respectively (Narod SA, data not published);
- tamoxifen use in spite of ER- breast cancer, because of 50% risk reduction of contralateral breast cancer [53, 60];
- adnexectomy not only because of prophylaxis but also because it was noted that 10-year survival is twice as high in patients after this type of treatment (Narod SA, data not published);
- breast cancer chemotherapy based on schemes without taxanes [61]; treatment results based on schemes with cis-platinum are very promising.

Syndromes associated with genetic changes of moderately increased risk

The essential problem of clinical genetics is increased hereditary predisposition to breast and ovarian cancer in families with negative history of these cancers. Because of the small number of family members in present families, inheritance by the male line and not full

Table 4. Scheme of control examinations in families with high breast/ovarian cancer syndromes

Organ	Examination	Age of beginning (years)	Frequency
Breast	self examination	20	every month
	medical palpation	20-25	every 6 months
	USG	25	every 6 months (6 months after mammography)
	MRI	25	every 12 months
	mammography	35	every 12 months
Female genital tract	transvaginal ultrasound	30-35	every 12 months
	CA 125	30-35	every 12 months (6 months after USG)

penetrance, the influence of high risk genes like *BRCA1/2* should be taken into consideration also in such families (about 50% of *BRCA1* mutation carriers with breast cancer come from unaffected families [20]). However, a clear majority of cancers in such families are associated with other factors. The influence of multiple environmental factors on cancer risk has already been documented in the past. Recently, it has been shown that over 90% of patients with breast cancer carry constitutional genetic changes predisposing to development of this cancer [62]. In most cases, they are changes of moderately increased risk. In that context we can suppose that unfavourable environmental factors could lead to cancer development only in patients with a particular genetic background. To date the significance of several genetic changes has been documented in the Polish population, which is the cause for different options of clinical management for these patients. It was found that constitutional changes in the genes *CHEK2* (1100delC, IVS2+1G>A, del5395, I157T), *NBS1* (657del5), *NOD2* (3020insC), *CDKN2A* (A148T), *BRCA2* (5972C/T polymorphism) and *CYP1B1* (homozygous GTC) are associated with increased breast cancer risk in the Polish population [63, 64]. Carrier status of protein truncated mutation in the *CHEK2* gene (1100delC, IVS2+1G>A, del5395) is associated with about 2.2-fold increased breast cancer risk. This risk concerns both young and older patients [63, 64]. Therefore, the control breast examination in this group of patients starts from 25 years of age according to the scheme shown in Table 5. Carriers of mutation *CHEK2* I157T have increased cancer risk to a smaller degree (1.4-fold higher than that in the general population). Occurrence of breast cancer at young age is not characteristic for this kind of mutation. However, patients with this mutation demonstrate lobular type of breast cancer much more often [65]. This cancer is difficult to diagnose using mammography; therefore in this group of patients magnetic resonance imaging (MRI) is recommended from 40 years of age. Mutation 657del5 in the *NBS1* gene is associated with about 3.5-fold increased risk of breast cancer and this increase is the strongest for patients below 40 years old [66] and with positive cancer family history [67]. Mutation 3020insC in the *NOD2* gene is associated with breast cancer at young age (OR=1.9). Characteristic for this mutation is ductal breast cancer with a DCIS component [68]. This kind of cancer is more often accompanied by multiple calcifications; therefore mammography can be useful in prophylaxis of patients with mutations in the *NOD2* gene. Polymorphism 5972C/T in the *BRCA2* gene is also associated with increased risk of breast cancer before 40 years of age (OR=1.4). The risk of cancer development is higher in homozygotes (OR=4.8). This effect is observed at both young and older age [69]. Increased risk is also observed in carriers of *CDKN2A* A148T (OR=1.5) and *CYP1B1* (homozygote GTC) (OR=1.5). In these cases an increased cancer risk at young age is observed. Medical care for patients with genetic changes *NBS1* (657del5), *NOD2* (3020insC), *BRCA2* (5972C/T), *CDKN2A* (A148T), and *CYP1B1* (homozygote GTC) begins at 25 years. Studies on the group of patients with a family history of ovarian cancer allowed characteristic clinical features of ovarian cancers without constitutional mutations in genes *BRCA1* and *BRCA2* to be

Table 5. Options of control examinations for carriers of moderate cancer risk gene mutations

Organ	Examination	Age of beginning (years)	Frequency
CHEK2 (1100delC, IVS2+1G>A, del5395), *NBS1* (657del5), *NOD2* (3020insC), *CDKN2A* (A148T)	self examination	20	every month
	medical palpation	20-25	every 6 months
	USG	25	every 12 months (6 months after mammography)
BRCA2 (5972C/T), *CYP1B1* (homozygote GTC)	mammography	35	every 12 months
CHEK2 (I157T)	self examination	20	every month
	medical palpation	40	every 6 months
	USG	40	every 12 months (6 months after mammography)
	MRI	40	every 12 months
	mammography	40	every 12 months

distinguished. Cancers in this group, unlike cases arising on the basis of *BRCA1* and *BRCA2* mutation, are more often diagnosed in postmenopausal (51-60 years) women and also show lower morphological grading and clinical staging. Analysis of the kind and location of cancers among relatives of examined women showed the increased frequency of ovarian cystadenoma (*cystadenoma ovarii*) [70]. Cystadenomas of the ovary are benign tumours which are able to, in some cases, undergo malignant transformation into borderline malignancy tumours, and sometimes even into cancer (*cystadenocarcinoma*) [71, 72]. For development of this kind of tumours the following constitutional changes can predispose: *NOD2* 3020insC, *CHEK2* I157T, *CYP1B1* 355T/T and *DHCR7* W151X. In the group of "increased risk" there are mainly women at reproductive age (≤50 years), who being carriers of at least one of the above-mentioned molecular changes have over twofold increased risk of the development of ovarian borderline malignancy tumours (OR 2.26, P=0.0005). Therefore for these women it should be considered to extend the screening options with an additional control examination of transvaginal USG (once a year) from 20-25 years. Early tumour detection and its surgical resection can prevent the development of ovarian cancer. Moreover, in the case of the 355T/T variant *CYP1B1* gene carriers the screening options are extended with an additional control examination for MRI of the breast (once a year) for women aged 30-35 years, on account of almost 3-fold increased risk of the development of cancer of this organ (OR 2.75, P=0.03) [73, 74]. The preventive screening is also recommended to first and second degree female relatives of patients with ovarian cystadenoma including:

- control examination by using transvaginal USG (once a year), if in the patient ovarian borderline malignancy tumour and *CHEK2* I157T were detected;
- control breast examination using MRI (once a year) in the case of female relatives of patients with the 355T/T variant of the *CYP1B1* gene and with benign ovarian tumour.

Studies on genetic predisposition to breast cancer or ovarian cystadenoma indicate the existence of multigenetic relations causing high risk of cancer development. It will probably require many years of analysis to discover them.

Summary

Around 14 000 women develop breast or ovarian cancer in Poland every year. Advances in clinical genetics of cancers allow a significant number of these cancers to be prevented. Additionally, patients of known genetic background may be more effectively diagnosed and treated due to the application of special, non-standard systems of control examinations and treatment.

References

1. Lynch HT. Genetics and breast cancer. Van Nostrand - Reinhold, New York 1981.
2. Broca P. Traite de tumeurs. Paris, Asselin 1866.
3. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W, Bell R, Rosenthal J, Hussey C, Tran T, McClure M, Frye C, Hattier T, Phelps R, Haugen-Strano A, Katscher A, Yakumo K, Gholami Z, Shaffer D, Stone S, Bayer S, Wray C, Bogden R, Dayananth P, Ward J, Tonin P, Narod SA, Bristow PK, Morris FH, Helvering L, Morrisom P, Rosteck P, Lai M, Barrett JC, Lewis C, Neuhausen S, Cannon-Albright L, Goldgar D, Wiseman R, Kamb A, Skolnick MH. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994; 266: 66-71.
4. Thompson D, Easton D; Breast Cancer Linkage Consortium. Variation in BRCA1 cancer risks by mutation position. Cancer Epidemiol Biomarkers Prev 2002; 11: 329-336.
5. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K. Environmental and heritable factors in the causation of cancer-analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000; 343: 78-85.
6. Swift M, Reitnauer PJ, Morrell D, Chase CL. Breast and other cancers in families with ataxia-telangiectasia. N Engl J Med 1987; 316: 1289-1294.
7. Antoniou AC, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjäkoski K, Kallioniemi OP, Thompson D, Evans C, Peto J, Lalloo F, Evans DG, Easton DF. Breast and ovarian cancer risks to carriers of the BRCA1 5382insC and 185delAG and BRCA2 6174delT mutations: a combined analysis of 22 population based studies. J Med Genet 2005; 42: 602-603.
8. Gronwald J, Huzarski T, Byrski B, Medrek K, Menkiszak J, Monteiro AN, Sun P, Lubinski J, Narod SA. Cancer risks in first degree relatives of BRCA1 mutation carriers: effects of mutation and proband disease status. J Med Genet 2006; 43: 424-428.
9. Risinger JI, Berchuck A, Kohler MF, Boyd J. Mutations of the E-cadherin gene in human gynecologic cancers. Nat Genet 1994; 7: 98-102.
10. Thorlacius S, Struewing JP, Hartge P, Olafsdottir GH, Sigvaldason H, Tryggvadottir L, Wacholder S, Tulinius H, Eyfjörd JE. Population-based study of risk of breast cancer in carriers of BRCA2 mutation. Lancet 1998; 352: 1337-1339.
11. Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, Van't Veer L, Garber JE, Evans G, Isaacs C, Daly MB, Matloff E, Olopade OI, Weber BL. The Prevention and Observation of Surgical End Points Study Group. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 2002; 346: 1616-1622.
12. Jakubowska A, Narod SA, Goldgar DE, Mierzejewski M, Masojć B, Nej K, Huzarska J, Byrski T, Górski B, Lubiński J. Breast cancer risk reduction associated with the RAD51 polymorphism among carriers of the BRCA1 5382insC mutation in Poland. Cancer Epidemiol Biomarkers Prev 2003; 12: 457-459.

13. Jakubowska A, Gronwald J, Menkiszak J, Górski B, Huzarski T, Byrski T, Edler L, Lubiński J, Scott RJ, Hamann U. The RAD51 135 G>C polymorphism modifies breast cancer and ovarian cancer risk in Polish BRCA1 mutation carriers. Cancer Epidemiol Biomarkers Prev 2007; 16: 270-275.
14. Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Kwan E, Jack E, Vesprini 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.
15. Marcus JN, Watson P, Page DL, Narod SA, Lenoir GM, Tonin P, Linder-Stephenson L, Salerno G, Conway TA, Lynch HT. Hereditary breast cancer: pathobiology, prognosis, and BRCA1 and BRCA2 gene linkage. Cancer 1996; 77: 697-709.
16. Martin AM, Blackwood MA, Antin-Ozerkis D, Shih HA, Calzone K, Colligon TA, Seal S, Collins N, Stratton MR, Weber BL, Nathanson KL. Germline mutations in BRCA1 and BRCA2 in breast-ovarian families from a breast cancer risk evaluation clinic. J Clin Oncol 2001; 19: 2247-2253.
17. Li FP, Fraumeni JF Jr. Soft-tissue sarcomas, breast cancer and other neoplasms. A familial syndrome? Ann Intern Med 1969; 71: 747-752.
18. Menkiszak J, Jakubowska A, Gronwald J, Rzepka-Górska I, Lubiński J. Hereditary ovarian cancer: summary of 5 years of experience. Ginekol Pol 1998; 69: 283-287.
19. Loman N, Johannsson O, Bendahl P, Dahl N, Einbeigi Z, Gerdes A, Borg A, Olsson H. Prognosis and clinical presentation of BRCA2-associated breast cancer. Eur J Cancer 2000; 36: 1365-1373.
20. Lubiński J, Górski B, Huzarski T, Byrski T, Gronwald J, Serrano-Fernández P, Domagała W, Chosia M, Uciński M, Grzybowska E, Lange D, Maka B, Mackiewicz A, Karczewska A, Breborowicz J, Lamperska K, Stawicka M, Gozdecka-Grodecka S, Bebenek M, Sorokin D, Wojnar A, Haus O, Sir J, Mierzwa T, Niepsuj S, Gugała K, Góźdź S, Sygut J, Kozak-Klonowska B, Musiatowicz B, Posmyk M, Kordek R, Morawiec M, Zambrano O, Waśko B, Fudali L, Skret J, Surdyka D, Urbański K, Mituś J, Ryś J, Szwiec M, Rozmiarek A, Dziuba I, Wandzel P, Wiśniowski R, Szczylik C, Kozak A, Kozłowski W, Narod SA. BRCA1-positive breast cancers in young women from Poland. Breast Cancer Res Treat 2006; 99: 71-76.
21. Lakhani SR. The pathology of familial breast cancer: Morphological aspects. Breast Cancer Res 1999; 1: 31-35.
22. Górski B, Byrski T, Huzarski T, Jakubowska A, Menkiszak J, Gronwald J, Płużańska A, Bębenek M, Fischer-Maliszewska L, Grzybowska E, Narod SA, Lubiński J. Founder mutations in the BRCA1 gene in Polish families with breast-ovarian cancer. Am J Hum Genet 2000; 66: 1963-1968.
23. Loman N, Johannsson O, Bendahl PO, Borg A, Fernö M, Olsson H. Steroid receptors in hereditary breast carcinomas associated with BRCA1 or BRCA2 mutations or unknown susceptibility genes. Cancer 1998; 83: 310-319.
24. Wooster R, Neuhausen SL, Mangion J, Quirk Y, Ford D, Collins N, Nguyen K, Seal S, Tran T, Averill D, Fields P, Marshall G, Narod SA, Lenoir GM, Lynch H, Feunteun J, Devilee P, Cornelisse CJ, Menko FH, Daly PA, Ormiston W, McManus R, Pye C, Lewis CM, Cannon-Albright LA, Peto J, Ponder BAJ, Skolnick MH, Easton DF, Goldgar DE, Stratton MR. Localisation of a breast cancer susceptibility gene BRCA2, to chromosome 13q12-13. Science 1994; 265: 2088-2090.
25. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 in a population based series of breast cancer cases. Br J Cancer 2000; 83: 1301-1308.
26. Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, Bishop DT, Weber B, Lenoir G, Chang-Claude J, Sobol H, Teare MD, Struewing J, Arason A, Scherneck S, Peto J, Rebbeck TR, Tonin P, Neuhausen S, Barkardottir R, Eyfjord J, Lynch H, Ponder BA, Gayther SA, Birch JM, Lindblom A, Stoppa-Lyonnet D, Bignon Y, Borg A, Hamann U, Haites N, Scott RJ, Maugard CM, Vasen H, Seitz S, Cannon-Albright LA, Schofield A, Zelada-Hedman M. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet 1998; 62: 676-689.
27. Hopper JL, Southey MC, Dite GS, Jolley DJ, Giles GG, McCredie MR, Easton DF, Venter DJ. Australian Breast Cancer Family Study. Population-based estimate of the average age-specific cumulative risk of breast cancer for a defined set of protein-truncating mutations in BRCA1 and BRCA2. Cancer Epidemiol Biomarkers Prev 1999; 8: 741-747.
28. Warner E, Foulkes W, Goodwin P, Meschino W, Blondal J, Paterson C, Ozcelik H, Goss P, Allingham-Hawkins D, Hamel N, Di Prospero L, Contiga V, Serruya C, Klein M, Moslehi R, Honeyford J, Liede A, Glendon G, Brunet JS, Narod SA. Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer. J Natl Cancer Inst 1999; 91: 1241-1247.
29. Jakubowska A, Nej K, Huzarski T, Scott RJ, Lubiński J. BRCA2 gene mutation in familie with aggregations of breast and stomach cancers. Br J Cancer 2002; 87: 888-891.
30. Jakubowska A, Scott R, Menkiszak J, Gronwald J, Byrski T, Huzarski T, Górski B, Cybulski C, Debniak T, Kowalska E, Starzyńska T, Ławniczak M, Narod S, Lubinski J. A high frequency of BRCA2 gene mutations in Polish families with ovarian and stomach cancer. Eur J Hum Genet 2003; 11: 955-958.
31. Kwiatkowska E, Teresiak M, Lamperska KM, Karczewska A, Breborowicz D, Stawicka M, Godlewski D, Krzyzosiak WJ, Mackiewicz A. BRCA2 germline mutations in male breast cancer patients in the Polish population. Hum Mutat 2001; 17: 73.
32. Boyd J, Sonoda Y, Federici MG, Bogomolniy F, Rhei E, Maresco DL, Saigo PE, Almadrones LA, Barakat RR, Brown CL, Chi DS, Curtin JP, Poynor EA, Hoskins WJ. Clinicopathologic features of BRCA-linked and sporadic ovarian cancer. JAMA 2000; 283: 2260-2265.
33. Malkin D, Li F, Strong L, Fraumeni J, Nelson C, Kim D, Kassel J, Gryka M, Bischoff M, Tainsky M, Friend S. Germline p53 mutations in a familar syndrome of breast cancer, sarcomas and other neoplasms. Science 1990; 250: 1233-1238.
34. Nelen MR, Padberg GW, Peeters EA, Lin AY, van den Helm B, Frants RR, Coulon V, Goldstein AM, van Reen MM, Easton DF, Eeles RA, Hodgsen S, Mulvihill JJ, Murday VA, Tucker MA, Mariman EC, Starink TM, Ponder BA, Ropers HH, Kremer H, Longy M, Eng C. Localization of the gene for Cowden disease to chromosome 10q22-23. Nat Genet 1996; 13: 114-116.
35. Hanssen AM, Fryns JP. Cowden syndrome. J Med Genet 1995; 32: 117-119.
36. Risinger JI, Barrett JC, Watson P, Lynch HT, Boyd J. Molecular geneic evidence of the occurrence of breast cancer as on integral tumor in patients with the hereditary nonpolyposis colorectal carcinoma syndrome. Cancer 1996; 77: 1836-1843.
37. Spigelman AD, Murday V, Phillips RK. Cancer and Peutz-Jeghers syndrome. Gut 1989; 30: 1588-1590.
38. Cohen MM Jr. A comprehensive and critical assessment of overgrowth and overgrowth syndromes. Adv Hum Genet 1989; 18: 181-303, 373-376.
39. Shiloh Y. Ataxia telangiectasia: closer to unraveling the mystery. Eur J Hum Genet 1995; 3: 116-138.
40. Lynch HT, Kaplan AR, Lynch JF. Klinefelter syndrome and cancer. A family study. JAMA 1974; 229: 809-811.
41. Wooster R, Mangion J, Eeles R, Smith S, Dowsett M, Averill D, Barrett-Lee P, Easton DF, Ponder BA, Stratton MR. A germline mutation in the androgen receptor in two brothers with breast cancer and Reifenstein syndrome. Nat Genet 1992; 2: 132-134.

42. Lindblom A, Sandelin K, Iselius L, Dumanski J, White I, Nordenskjöld M, Larsson C. Predisposition for breast cancer in carriers of constitutional translocation 11q;22q. Am J Hum Genet 1994; 54: 871-876.
43. Narod SA, Risch H, Moslehi R, Dorum A, Neuhausen S, Olsson H, Provencher D, Radice P, Evans G, Bishop S, Brunet JS, Ponder BA. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. N Engl J Med 1998; 339: 424-428.
44. McLaughlin JR, Risch HA, Lubiński J, Moller P, Ghadirian P, Lynch H, Karlan B, Fishman D, Rosen B, Neuhausen SL, Offit K, Kauff N, Domchek S, Tung N, Friedman E, Foulkes W, Sun P, Narod SA, Hereditary Ovarian Cancer Clinical Study Group. Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. Lancet Oncol 2007; 8: 26-34.
45. Narod SA, Dube MP, Klijn J, Lubiński J, Lynch HT, Ghadirian P, Provencher D, Heimdal K, Moller P, Robson M, Offit K, Isaacs C, Weber B, Friedman E, Gershoni-Baruch R, Rennert G, Pasini B, Wagner T, Daly M, Garber JE, Neuhausen SL, Ainsworth P, Olsson H, Evans G, Osborne M, Couch F, Foulkes WD, Warner E, Kim-Sing C, Olopade O, Tung N, Saal HM, Weitzel J, Merajver S, Gauthier-Villars M, Jernstrom H, Sun P, Brunet JS. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 2002; 94: 1773-1779.
46. Grabrick DM, Hartmann LC, Cerhan JR, Vierkant RA, Therneau TM, Vachon CM, Olson JE, Couch FJ, Anderson KE, Pankratz VS, Sellers TA. Risk of breast cancer with oral contraceptive use in women with a family history of breast cancer. JAMA 2000; 284: 1791-1798.
47. Armstrong K, Schwartz JS, Randall T, Rubin SC, Weber B. Hormon replacement therapy and life expectancy after prophylactic oophorectomy in women with BRCA1/2 mutations: a decision analysis. J Clin Oncol 2004; 22: 1045-1054.
48. Rebbeck TR, Friebel T, Wagner T, Lynch HT, Garber JE, Daly MB, Isaacs C, Olopade OI, Neuhausen SL, van 't Veer L, Eeles R, Evans DG, Tomlinson G, Matloff E, Narod SA, Eisen A, Domchek S, Armstrong K, Weber BL. Effect of Short-Term Hormone Replacement Therapy on Breast Cancer Risk Reduction After Bilateral Prophylactic Oophorectomy in BRCA1 and BRCA2 Mutation Carriers: The PROSE Study Group. J Clin Oncol 2005; 23: 7804-7810.
49. Buchet-Poyau K, Mehenni H, Radhakrishna U, Antonarakis SE. Search for the second Peutz-Jeghers syndrome locus: exclusion of the STK13, PRKCG, KLK10, and PSCD2 genes on chromosome 19 and the STK11IP gene on chromosome 2. Cytogenet Genome Res 2002; 97: 171-178.
50. Gronwald J, Byrski T, Huzarski T, Cybulski C, Sun P, Tulman A, Narod SA, Lubinski J. Influence of selected lifestyle factors on breast and ovarian cancer risk in BRCA1 mutation carriers from Poland. Breast Cancer Res Treat 2006; 95: 105-109.
51. Narod SA. Hormonal prevention of hereditary breast cancer. Ann N Y Acad Sci 2001; 952: 36-43.
52. Kotsopoulos J, Lubinski J, Lynch HT, Klijn J, Ghadirian P, Neuhausen SL, Kim-Sing C, Foulkes WD, Moller P, Isaacs C, Domchek S, Randall S, Offit K, Tung N, Ainsworth P, Gershoni-Baruch R, Eisen A, Daly M, Karlan B, Saal HM, Couch F, Pasini B, Wagner T, Friedman E, Rennert G, Eng C, Weitzel J, Sun P, Narod SA; Hereditary Breast Cancer Clinical Study Group, Garber J, Osborne M, Fishman D, McLennan J, McKinnon W, Merajver S, Olsson H, Provencher D, Pasche B, Evans G, Meschino WS, Lemire E, Chudley A, Rayson D, Bellati C. Age at first birth and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat 2007; 105: 221-228.
53. Gronwald J, Tung N, Foulkes W, Offit K, Gershoni R, Daly M, Kim-Sing C, Olsson H, Ainsworth P, Eisen A, Saal H, Friedman E, Olopade O, Osborne M, Weitzel J, Lynch H, Ghadirian P, Lubiński J, Sun P, Narod SA; Hereditary Breast Cancer Clinical Study Group. Tamoxifen and contralateral breast cancer in BRCA1 and BRCA2 carriers: an update. Int J Cancer 2006; 118: 2281-2284.
54. Narod SA, Brunet JS, Ghadirian P, Robson M, Heimdal K, Neuhausen SL, Stoppa-Lyonnet D, Lerman C, Pasini B, de los Rios P, Weber B, Lynch H, Hereditary Breast Cancer Clinical Study Group. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Hereditary Breast Cancer Clinical Study Group. Lancet 2000; 356: 1876-1881.
55. Kowalska E, Narod SA, Huzarski T, Zajaczek S, Huzarska J, Gorski B, Lubinski J. Increased rates of chromosome breakage in BRCA1 carriers are normalized by oral selenium supplementation. Cancer Epidemiol Biomarkers Prev 2005; 14: 1302-1306.
56. Menkiszak J, Rzepka-Górska I, Górski B, Gronwald J, Byrski T, Huzarski T, Jakubowska A, Metcalfe KA, Narod SA, Lubiński J. Attitudes toward preventive oophorectomy among BRCA1 mutation carriers in Poland. Eur J Gynaecol Oncol 2004; 25: 93-95.
57. Zeigler LD, Kroll SS. Primary breast cancer after prophylactic mastectomy. Am J Clin Oncol 1991; 14: 451-454.
58. Temple WJ, Lindsay RL, Magi E, Urbanski SJ. Technical considerations for prophylactic mastectomy in patients at high risk for breast cancer. Am J Surg 1991; 161: 413-415.
59. Warner E, Plewes DB, Shumak RS, Catzavelos GC, Di Prospero LS, Yaffe MJ, Goel V, Ramsay E, Chart PL, Cole DE, Taylor GA, Cutrara M, Samuels TH, Murphy JP, Murphy JM, Narod SA. Comparison of breast magnetic resonance imaging, mammography, and ultrasound for surveillance of women at high risk for hereditary breast cancer. J Clin Oncol 2001; 19: 3524-3531.
60. Narod SA, Dubé MP, Klijn J, Lubinski J, Lynch HT, Ghadirian P, Provencher D, Heimdal K, Moller P, Robson M, Offit K, Isaacs C, Weber B, Friedman E, Gershoni-Baruch R, Rennert G, Pasini B, Wagner T, Daly M, Garber JE, Neuhausen SL, Ainsworth P, Olsson H, Evans G, Osborne M, Couch F, Foulkes WD, Warner E, Kim-Sing C, Olopade O, Tung N, Saal HM, Weitzel J, Merajver S, Gauthier-Villars M, Jernstrom H, Sun P, Brunet JS. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 2002; 94: 1773-1779.
61. Byrski T, Gronwald J, Huzarski T, Grzybowska E, Budryk M, Stawicka M, Mierzwa T, Szwiec M, Wiśniowski R, Siołek M, Narod SA, Lubiński J, the Polish Hereditary Breast Cancer Consortium. Response to neo-adjuvant chemotherapy in women with BRCA1-positive breast cancers. Breast Cancer Res Treat 2008; 108: 289-296.
62. Lubiński J, Korzeń M, Górski B, Cybulski C, Dębniak T, Jakubowska A, Jaworska K, Wokołorczyk D, Mędrek K, Matyjasik J, Huzarski T, Byrski T, Gronwald J, Masojć B, Lener M, Szymańska A, Szymańska-Pasternak J, Serrano-Fernández P, Piegat A, Uciński R, Domagała P, Domagała W, Chosia M, Kładny J, Górecka B, Narod S, Scott R. Genetic contribution to all cancers: the first demonstration using the model of breast cancers from Poland stratified by age at diagnosis and tumour pathology. Breast Cancer Res Treat 2008 Apr 15 [Epub ahead of print].
63. Cybulski C, Górski B, Huzarski T, Byrski T, Gronwald J, Debniak T, Wokolorczyk D, Jakubowska A, Kowalska E, Oszurek O, Narod SA, Lubinski J. CHEK2-positive breast cancers in young Polish women. Clin Cancer Res 2006; 12: 4832-4835.
64. Cybulski C, Wokołorczyk D, Huzarski T, Byrski T, Gronwald J, Górski B, Dębniak T, Masojć B, Jakubowska A, van de Wetering T,

Narod SA, Lubiński J. A deletion in CHEK2 of 5,395 bp predisposes to breast cancer in Poland. Breast Cancer Res Treat 2007; 102: 119-122.
65. Huzarski T, Cybulski C, Domagała W, Gronwald J, Byrski T, Szwiec M, Woyke S, Narod SA, Lubiński J. Pathology of breast cancer in women with constitutional CHEK2 mutations. Breast Cancer Res Treat 2005; 90: 187-189.
66. Steffen J, Nowakowska D, Niwińska A, Czapczak D, Kluska A, Piątkowska M, Wiśniewska A, Paszko Z. Germline mutations 657del5 of the NBS1 gene contribute significantly to the incidence of breast cancer in Central Poland. Int J Cancer 2006; 119: 472-475.
67. Górski B, Debniak T, Masojć B, Mierzejewski M, Medrek K, Cybulski C, Jakubowska A, Kurzawski G, Chosia M, Scott R, Lubiński J. Germline 657del5 mutation in the NBS1 gene in breast cancer patients. Int J Cancer 2003; 106: 379-381.
68. Huzarski T, Lener M, Domagała W, Gronwald J, Byrski T, Kurzawski G, Suchy J, Chosia M, Woyton J, Uciński M, Narod SA, Lubiński J. The 3020insC allele of NOD2 predisposes to early-onset breast cancer. Breast Cancer Res Treat 2005; 89: 91-93.
69. Górski B, Narod SA, Lubiński J. A common missense variant in BRCA2 predisposes to early onset breast cancer. Breast Cancer Res 2005; 7: R1023-R1027.
70. Menkiszak J, Gronwald J, Górski B, Byrski T, Huzarski T, Jakubowska A, Foszczynska-Kloda M, Brzosko M, Fliciński J, Rzepka-Gorska I, Narod SA, Lubiński J. Clinical features of familial ovarian cancer lacking mutations in BRCA1 or BRCA2. Eur J Gynaecol Oncol 2004; 25: 99-100.
71. Hart WR. Mucinous tumors of the ovary: A review. Int J Gynecol Pathol 2005; 24: 4-25.
72. Shih IeM, Kurman RJ. Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. Am J Pathol 2004; 164: 1511-1518.
73. Szymańska A. Identyfikacja genów związanych z predyspozycją do gruczolako-torbielaków śluzowych jajnika. Doctor's thesis. Pomorska Akademia Medyczna, Szczecin 2006.
74. Szymańska-Pasternak J. Identyfikacja genów związanych z predyspozycją do gruczolako-torbielaków surowiczych jajnika. Doctor's thesis. Pomorska Akademia Medyczna, Szczecin 2007.