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Hereditary breast and ovarian cancer

Dziedziczny rak piersi i jajnika

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Summary

Recently, it is possible to show a constitutional genetic background in almost all patients with breast or ovarian cancer. It has been recognized that increased risk of breast cancers occurs in carriers of mutations in *BRCA1*, *BRCA2*, *PALB2*, *RAD51*, *RAD51C*, *TP53*, *MSH6*, *MRE11A*, *CDH1*, *CHEK2*, *NBS1*, *NOD2*, *CDKN2A*, *CYP1B1* and less frequently of genes such as *ATM*, *PTEN*, *STK11*. Abnormalities in *BRCA1*, *BRCA2*, *NOD2*, *CHEK2*, *DHCR7* genes are predisposing factors also for development of ovarian cancer. In some cases, characteristic gene mutations are related to a very high risk of cancer, in other cases detected genetic changes predispose to cancer at lower degree. Diagnosis of increased risk of cancer allows introduction of prophylactic programs which make possible to avoid cancer, or diagnose it in early stages. Additionaly, the most effective method of treatment can be chosenfor carriers of some mutations. Significant diagnostic problem constitute patients in whom molecular abnormality was not detected but pedigree-clinical data indicate strong genetic background of cancer.

In the review we show the genetic background of breast and ovarian cancer taking into consideration contribution of high and moderate penetrance genes as well as importance of pedigree data. We discuss rules of diagnosis, prophylactics, the most sensitive methods of early detection and treatment in patients with *BRCA1*, *BRCA2* and other high risk syndromes as well as in patients with abnormalities in moderate penetrance genes.

Streszczenie

W ostatnich latach udało się wykazać u niemal wszystkich pacjentek z rakami piersi lub jajnika charakterystyczne podłoże konstytucyjne sprzyjające rozwojowi tych nowotworów. Stwierdzono, że nosicielstwo mutacji w genach *BRCA1*, *BRCA2*, *CHEK2*, *NBS1*, *NOD2*, *CDKN2A*, *CYP1B1*, jak i rzadziej występujących zmian w genach takich jak *ATM, PTEN, STK11* wiąże się z podwyższonym ryzykiem raka piersi. Zaburzenia w genach *BRCA1*, *BRCA2*, *NOD2*, *CHEK2*, *DHCR7* predysponują do rozwoju raka jajnika. W niektórych przypadkach zmiany genetyczne wiążą się z bardzo wysokim ryzykiem nowotworowym, w innych przypadkach wykrywane zaburzenia predysponują do rozwoju raka w mniejszym stopniu. Zdiagnozowanie podwyższonego ryzyka raka umożliwia wdrożenie programu profilaktycznego umożliwiającego zapobieżenie nowotworowi, a tam gdzie to się nie udaje, pozwala na wykrycie raka we wczesnym stadium. Dodatkowo zdiagnozowanie nosicielstwa odpowiednich mutacji pozwala na dobór najefektywniejszego, zindywidualizowanego sposobu leczenia związanego z uwarunkowaniami konstytucjonalnymi pacjenta. Dużym problemem diagnostycznym są pacjentki, u których nie udało się znaleźć zmian molekularnych, ale dane rodowodowo-kliniczne wskazują na silne podłoże genetyczne nowotworu.

W niniejszym opracowaniu przedstawiono podłoże genetyczne rozwoju raka piersi i jajnika, uwzględniając wpływ genów wysokiego oraz umiarkowanie zwiększonego ryzyka oraz zasady interpretacji danych rodowodowych. Omówiono obecnie obowiązujące zasady diagnozowania grup ryzyka, profilaktyki oraz leczenia raka u pacjentek ze zmianami w genach *BRCA1*, *BRCA2* oraz innymi zespołami wysokiego ryzyka, jak również ze zmianami w genach umiarkowanie zwiększonego ryzyka.

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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 nineties it was proven at molecular level that substantial number of breast and ovarian cancers has hereditary monogenic etiology (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 tweens indicate that about 30% of breast and ovarian cancers develop because of strong genetic predisposition (5). In other breast/ovarian cancers significance of genetic factors was underestimated. However, recently it was possible to show characteristic constitutional baground influencing development of cancer also in patients with sporadic neoplasms. Therefore now, scientists think that in almost all patients with cancer a certain genetic backgroung should be detectable although influencing cancer risk with different degree. Genetic abnormalities strongly related with cancer are called high risk changes (genes) and abnormalities influencing cancer development with lower degree are called moderate risk changes (genes). In Polish population most frequently strong genetic predisposition to breast/ovarian cancers are related to mutations in *BRCA1*, *CHEK2* or *PALB2* genes. Mutations in *BRCA2* gene are observed relatively rare. Mutations in these genes most often apeare 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 with 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 the discussed syndromes are summarized in table 1. In vast majority of cancer cases related to moderate risk genes family history is negative. HBC-ss, HBOC, HOC syndromes are clinically and molecullary heterogenous. Mutations in *BRCA1* and *BRCA2* genes are the most frequent cause of these syndromes. Recently, it was shown that in substantial number of such families, the syndrome develop because of truncating mutations in *CHEK2* gene or *PALB2* genes (6, 7).

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

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 I° relatives (or II° through male line) 2. 1 breast cancer and 1 ovarian cancer diagnosed at any age among I° relatives (or II° 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. Triple negative breast cancer 5. Breast and ovarian cancer in the same person 6. 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% life-time risk of breast cancer and 40% risk of ovarian cancer (8). We estimate that these risks are 66% for breast cancer and 44% for ovarian cancer in the Polish population (tab. 2). Both risks appear to be dependent on the type and localization of the mutation (9-11). Our findings suggest that the risk of breast cancer in women with 5382insC is two times higher than in women with 4153delA (9). Another factor affecting the level of risk is the degree of burden of family history. It was found that the risk of breast cancer increases by a further 20% with development of breast cancer before the age of 50 in each I° relative. In contrast, the occurrence of ovarian cancer each I° or II° relative is associated with an increased risk of ovarian cancer by a further 60% (12). Also the place of residence affect the level of the risk. In a recent prospective study found differences in penetration depending on place of residence. And so, the likelihood of developing breast cancer up to 70 years of age for the *BRCA1* gene mutation carriers in North America set at 72%, and for the Polish carriers to 49%, indicating the importance of environmental factors (13).

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

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

Incomplete penetrance of *BRCA1* suggests that other factors, genetic and non-genetic modifiers are important in carcinogenesis in the mutation carriers.

So far, several changes with potential significance in modification of the cancer risk have been identified. Multicenter study of CIMBA consortium suggest that these changes alone are weak and likely the effect is variable in different populations (14-29).

Characteristic for *BRCA1* carriers is, that except ovarian cancer, it is also also heightened risk of the fallopian tube and peritoneal cancers, estimated at about 10%. The above data on the incidence of ovarian cancer is likely to relate to the incidence of cancers of the ovary, fallopian tube, and peritoneal because these tumors were in the past, the most frequently diagnosed as ovarian cancers due to the similar morphology and the accompanying increase in the level of the marker CA 125.

The risk of cancer to other organs in some types of *BRCA1* is also increased, but the effect of carrying a *BRCA1* dysfunction has not yet been definitively proven.

Breast and ovarian cancer in *BRCA1* carriers have particular clinical characteristics. The mean age at onset of breast cancer is about 42-45 years (30, 31) and of ovarian cancer is about 54 years (32, 33). 18-32% of breast cancers are bilateral (34, 35). These are rapidly growing tumors: > 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°. Medullar, atypical medullar, ducal and estrogen receptor negative (ER-) breast tumors are common in *BRCA1* carriers. BRCA1-dependent breast cancers account for about 25-30% of all cancers triple-negative (ER-, PGR-, HER2-), however in *BRCA1*-dependent tumors positive ER is observed in 10-15% of cases (34-36). Most carriers of a *BRCA1* mutation report a positive family history of breast or ovarian cancer (fig. 1). However, 45% of *BRCA1* carriers report a negative family history, mainly because of paternal inheritance and incomplete penetrance (fig. 2) (35).

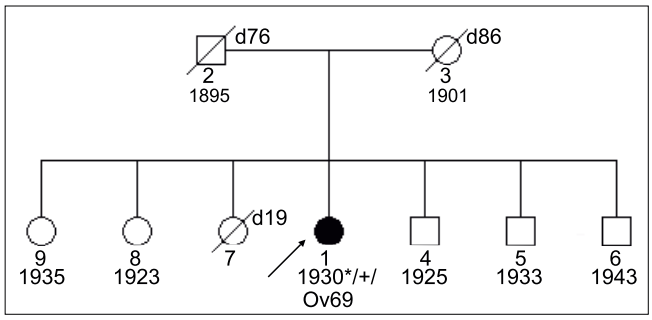

Fig. 2. Patent with ovarian cancer and detected 5382insC *BRCA1* mutation from family with negative family history.

BRCA2 SYNDROME

Patients with this syndrome have constitutional mutation in *BRCA2* gene (5). According to literature data life time risk for *BRCA2* carries from families with definitive HBC-ss and HBOC is estimated on 31-56% for breast cancer and 11-27% for ovarian cancer (10, 39-43). Studies performed in 200 Polish families with strong aggregation of breast and/or ovarian cancers proved that mutations in *BRCA2* gene are rare with the frequency of 4%. There are no studies on cumulated cancer risk in *BRCA2* mutation carriers form Polish population. Most *BRCA2* mutations from Polish population most probably slightly increase breast cancer risk. Studies performed in our center showed that in families with aggregation of breast cancer diagnosed before age of 50 and stomach cancer diagnosed in males before age of 55 frequency of *BRCA2* carriers is about 10-20% (44). *BRCA2* mutations are related also with significantly increased however not precisly estimated risk of ovarian cancer and cancers of digestive tract as stomach, colon, pancreas both in females and males. Studies performd in our center showed *BRCA2* mutation are detected with 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 (45). *BRCA2* studies performed on male breast cancer patients from Poznań population showed that 15% of patients from this group are mutation carriers (46).

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 of ovarian cancer (46, 47).

OTHER HIGH RISK BREAST CANCER SYNDROMES

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

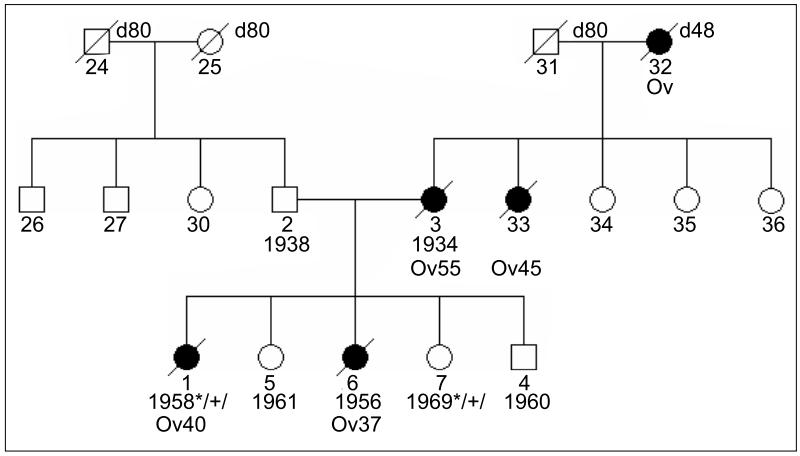

Fig. 1. Family with HOC syndrome and diagnosed constitutional 4153delA *BRCA1* gene mutation.

possible to diagnose one of rare syndromes listed in table 3. In these syndromes breast/ovarian cancers are observed with higher frequency. Many groups in the world try to identify new genes related to high breast cancer risk.

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 risk; usually around 50% of female family members shoud be included into program,
- all family members of families with HBC-ss, HBOC, 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:
a) prophylactics,
b) surveillance,
c) treatment.

Ad. a. Prophylactics

Oral conrtaceptives

Contrindications for using oral contraceptives (OC) by *BRCA1* carriers at age below 25 are well documented.

It has been shown that OC applied at an early age (< 25) by five years increase the risk of breast cancer by about 40%, and breast cancer occurring up to 40 years of age up to about 74% (61, 62). Since about 30% of *BRCA1* does not state any features HBC-ss, HBOC or HOC, it seems necessary to make a *BRCA1* test in every young woman who consider oral contraceptives. Contraceptives used by *BRCA1* mutation carriers after age 30 does not seem to affect the growth of breast cancer risk (61-64), while the decrease of approximately 50% risk of ovarian cancer (61). Thus, their use in later life seems to be justified.

Up to now, there are no verified data concerning 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 (65), thus it seams reasonable to avoid OC in families with HBC-ss and/or HBOC.

Hormonal replacement therapy (HRT)

Prophylactic oopherectomy at age of 35-40 is 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 estrogen HRT show similar protective effect like patients who do not use HRT (66-68). Influence of HRT in carriers without prophylactic oopherectomy is not well documented. 3-fold increased risk of breast cancer in HRT users with positive breast cancer family history was reported (69). Therefore, decision about HRT use shoud be taken with particular caution.

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

Disease	Clinics	Gene mutation/inheritance	Referencer
Li-Fraumeni syndrome	Breast cancers, sarcomas, brain tumours, leukemia, arenal gland cancer	p53, high penetrance; AD	47, 48
Cowden disease	Multifocal mucoid skin abnormalities, benign proliferative abnormalities of different organs, thyroid cancers, breast/ovarian cancers	PTEN AD	49, 50
HNPCC	Colon cancers, endometrial cancers, other organ cancers including breast and ovary	*MSH2*, *MLH1*; AD	51
Peutz-Jeghers syndrome	Hyperpigmentation of the mouth, bowel polyps, colorectal cancers, small bowel cancers, gonadal tumors, breast cancers	STK11; AD	52
Ruvalcaba-Myhre-Smith (Bannayan-Riley-Ruvalcaba) syndrome	Macrocephaly, bowel polyps, "café-au-lait" on penis, lyphomas, thyroid cancers, breast cancers	PTEN AD	53
Heterozygotic carrier status of "ataxia telangiectasia" gene	Ataxia of cerebellum, ocular and skin, hypersensitivity for radiation, different site neoplasm including breast/ovarian cancer	ATM penetrance 20-40% AD	54, 55
Klinefelter syndrome	Gynecomastia, cryptorchidism, extragonadal germ cell tumors, male breast cancer	47, XXY; low penetrance < 10%	56
Androgene receptor gene mutation	Familial male breast cancer	Androgene receptor	57
PALB2 gene mutation	High risk of brest cancer	*PALB2* penetrance ~30%	7
Coexistence of *CHEK2* gene mutation and polymorphism B2P1	High risk of developing breast cancer, and moderately increased risk of cancer of the colon, kidney, thyroid, prostate	*CHEK2*/*B2P1* penetrance ~30-40%	58
CHEK2 gene mutation in patients with a family history of breast cancer	High risk of developing breast cancer, and moderately increased risk of cancer of the colon, kidney, thyroid, prostate	*CHEK2* penetrance ~30-40%	59, 60
Homozygous mutation in the gene *CHEK2*	High risk of developing breast cancer, and moderately increased risk of cancer of the colon, kidney, thyroid, prostate	*CHEK2* penetrance ~30-40%	60

Inheritance: AD – autosomal dominant; AR – autosomal recessive

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 togother all pregnancies, is reducing breast cancer risk – from 50-80% to 25-40% (69, 70).

Early delivery

Women from general population who delivered the first child before age of 20 are of 50% lower breast cancer risk than nullparous women. This observation was not confirmed in women with *BRCA1* or *BRCA2* mutation (71). However taking into consideration the fact that mutation carriers should elect prophylactic oopherectomy at age of 35-40, they shold not delay maternity significantly.

Chemoprevention

Tamoxifen

Literature data cleary indicate that tamoxifen decreases about 50% risk of ER+ breast cancers. This effect was observed in healty women as well as in women treated because of breast cancer where tamoxifen decreased risk of contralateral breast cancer. Protective effect of tamoxifen was observed also in *BRCA1* carriers in spite of the fact that most cancers in these patients are ER-. Such effect of tamoxifen was observed in pre- and postmenopausal women (71-73). According to present data it is justified to propose 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. Current results indicate that the annual use of tamoxifen has a similar effect as a preventive therapy of 5-year (74).

Micronutrients

In December 2008, unblinded data conducted by our center, double-blind clinical trial on the effects of selenium on the risk of cancer in *BRCA1* mutation carriers. In an attempt was attended by more than 1300 women who have unexpectedly found that sodium selenite supplemented subgroup, after nearly 3 years of the trial there was slightly greater number of breast and ovarian cancer. Association studies suggest that carriers of *BRCA1* optimum level to determine the genotypes of selenium selenium metabolizing genes. So far, the strongest association found for *GPX1* gene. For carriers of rs1050450 genotype CC reduced risk of cancers found at the plasma selenium concentration > 80 μg/l. Opposite nCC genotype is associated with a decreased risk of cancer at the level of selenium in the plasma < 80 μg/l. We started a prospective observational study on the possibility of reducing the risk of breast cancer and/or ovarian in *BRCA1* carriers by optimizing the content of selenium in the diet/body in accordance with the results of association studies. The ability to reduce the risk of cancer in carriers of *BRCA1* through supplementation with selenium and low selenium diet requires further study, but already can be used to determine the level of selenium in plasma as a marker for the risk of breast and/or ovarian cancer in *BRCA1* carriers. Recently published reports indicating the importance of iron and antimony on the risk of breast cancer in *BRCA1* gene mutation carriers (75).

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 togother with tamoxifen reduces brast cancer risk to about 10% in *BRCA1* carriers (76). Therefore, in our center adnexectomy is recommended to all *BRCA1/2* carriers at age over 35. Recently it has been shown that prophylactic adnexectomy is associated with an 80% reduction in the incidence of cancer of the ovary, oviduct and the peritoneum and 77% reduction in mortality resulting from any cause (77). In view of the above facts in our center prophylactic adnexectomy is recommended to all *BRCA1/2* carriers, which are over 35 years of age. 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 femal genital tract were recorded during control examinations. About 85% of our patients accept this type of prophylactics (78).

Mastectomy

The main target of prophylactic mastectomy is reduction of breast cancer risk by removal of tissue at risk. Single cases of breast cancers can develop from chest wall or from axillary cave after prophylactic mastectomy. It was noted, however that only 1% patients from this group develop breast cancer after prophylactic surgery (79). It seams resonable to offer this type of surgery for highly motivated patients with definitively diagnosed high cancer risk, especially where tumoral and mammographically dense breast glands are observed which make early diagnosis extremely difficult. At present, mastectomies with immidiate reconstruction are performed most frequently. This procedure ensures good cosmetic effect (80).

Ad. b. Surveillance

Surveillance in patients with HBC-ss, HBOC, HOC, as well as in *BRCA1*/*BRCA2* carriers is show in table 4. This scheme is individualized for particular patients with respect to age when particural examinations shoud begin. In some families where breast cancer was diagnosed before age of 25 or ovarian cancer before age of 35 surveillance should begin 5 years earlier than age of diagnosis of cancer in this family. In some cases, in addition to breast and ovary investigations

patients receive coloscopy, gastroscopy or evaluation of PSA level and prostate ultrasound if in family members symptoms from colon, gastric or urinal tract are observed. However, it should be noted that some control examinations have limited value in detection od early cancers in *BRCA1* carriers. Ovarian cancer in clinical stage I is detected in only 10% of women with *BRCA1* mutation. On the other hand, magnetic resonanse in diagnosis of early breast cancers is introducting significant progress (30, 65). This examination allows detection of 77% of breast cancer with diameter smaller than 1 cm and in combination with ultrasound its sensitivity in detection of early breast cancers is rising to over 90% in *BRCA1* carriers (81). You should be aware that even with the extended regimen checkups in 10-15% of patients at diagnosis of breast cancer metastases to the axillary nodes.

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 mammogrophy)
	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)

Ad. c. 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 tharaphy, because risk of local recurrence is in above procedures 1% and 8%, respectively (Narod SA, unpublished data),
- tamoxifen use in spite of ER- breast cancer, because of 50% risk reduction of contralateral breast cancer (72-74),
- adnexectomy not only due to the prevention of ovarian cancer, but also because this treatment reduces the risk of death within 10 years by 70% (82),
- in the case of breast cancer patients treated with chemotherapy demonstrated significantly better schemes without taxanów (83). Extremely interesting are the results of the use of neoadjuvant cisplatin in the treatment of patients with breast cancer (84, 85). In the group of 107 *BRCA1* complete pathological tumor remission was achieved in approximately 61% of patients. The treatment results were slightly better (69% of patients with pathologic complete remission, if prior to the application of cisplatin patients were treated with other chemotherapeutic agents. The treatment effect to some extent depends on the tumor stage. The pathological complete remission was observed in 56% of patients with breast cancer diagnosed in clinical stage IIB-III, whereas in 78% of patients whose cancer was diagnosed with stage I-II. High effectiveness of cisplatin was also observed in the treatment of a patient with metastatic breast cancer (86). At the same time are ongoing clinical trials using PARP inhibitors to treat *BRCA1* breast cancer or ovarian cancer. It was recently discovered that *BRCA1* mutation carriers with breast cancer diagnosed in the clinical stage I are benefiting if the surgery was completed with chemotherapy compared to patients who did not receive chemotherapy (HR = 0.28; 95% CI 0.10-0.79; p = 0.02) (87).

THE SYNDROMES ASSOCIATED WITH GENETIC CHANGES OF MODERATE 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 small number of family members in present families, inheritance by male line and not full penetrance, 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) (33). However, the straight majority of cancers in such families are associated with other factors. The influence of multiple environmental factors on cancer risk was already documented in the past. Recently, it has been shown that above 90% of patients with breast cancer carry the constitutional genetic changes predisposing to development of this cancer (88). In the most cases, there are changes of the moderately in increased risk. In that context we can suppose that unfavorable environmental factors could lead to cancer development only in the patients with particular genetic background. To date the significance of several genetic changes has been documented in Polish population, what is the cause for different options of clinical management for these patients. It was found that constitutional changes in genes: *CHEK2* (1100delC, IVS2+1G>A, del5395, I157T), *NBS1* (657del5), *NOD2* (3020insC), *CDKN2A* (A148T), *BRCA2* (5972C/T polymorphism), *CYP1B1* (homozygous GTC) are associated with increased breast cancer risk in Polish population (89, 90).

Carrier status of protein truncated mutation in *CHEK2* gene (1100delC, IVS2+1G>A, del5395) is associated with about 3-fold increased breast cancer risk, what is even more important as many as 5-7-fold increase in families with breast cancers among relatives (6, 59, 60). Cybulski et al. determined that the risk of breast cancer in carriers of *CHEK2* protein truncating mutations is 28% if the breast cancer occurred in second degree relative, 34% if breast cancer occurred in relative I^{o} and

44% when breast cancer was diagnosed in I° and second degree relative (60). Therefore, *CHEK2* mutation carriers that meet these criteria should be considered as high-risk patients. This risk applies to both young and older patients. Thus, the control breast examination in this group starts from 25 years of age (tab. 5).

I157T type *CHEK2* mutation carriers are at elevated risk to a lesser extent (1.4-fold higher than the general population). The occurrence of breast cancer at a young age is not a characteristic feature of this type of mutation, therefore in this group of patients breast examinations start in age of 40 (tab. 5). It was found, however, that patients with this mutation significantly more common develop lobular type of breast cancer (91). This tumor is difficult to detect only by mammography. Recently it has been shown that the combination of breast ultrasound and mammography applied in that the group of patients similar to the sensitivity of magnetic resonance imaging (personal communication, sent to the publication). In this context, taking into account the costs of examinations, breast ultrasound with mammography seem to be a reasonable alternative to breast MRI.

Recently it has been found that the carrier *PALB2* gene mutation is associated with approximately 5-fold increase in risk of breast cancer, and these tumors are characterized with worse prognosis (7).

The mutation in *NBS1* gene (657del5) is associated with about 3.5-fold increase risk of breast cancer and this increase is the strongest for patients below 40 yrs (92) and positive cancer family history (93). Mutation 3020insC in *NOD2* gene is associated with breast cancer at young age (OR = 1.9). Characteristic for this mutation is ductal breast cancer with DCIS component (94). This kind of cancer is more often accompanied by multicalcifications, therefore mammography can be useful in prophylactics of patients with mutations in *NOD2* gene. Polymorphism 5972C/T in *BRCA2* gene is also associated with increased risk of breast cancer before 40 yrs (OR = 1.4). The risk of cancer development is higher in the homozygotes (OR = 4.8). This effect is observed both at young and older age (92). The increased risk is also observed in carriers of *CDKN2A* A148T (OR = 1.5) and *CYP1B1* (homozygote GTC) (OR = 1.5). In these cases it is observed the increase of cancer risk at young age. The medical care for patients with genetic changes: *NBS1* (657del5), *NOD2* (3020insC), *BRCA2* (5972C/T), *CDKN2A* (A148T), *CYP1B1* (homozygote GTC) begins at 25 yrs according to sheme included in the table 5.

Studies on the group of patients with the family history of the ovarian cancer allowed distinguishing characteristic clinical features of ovarian cancers without constitutional mutations in *BRCA1* and *BRCA2* genes. Cancers in this group, unlike cases arising on the basis of the *BRCA1* and *BRCA2* mutation, are more often diagnosed in the postmenopausal (between 51-60 yrs) women and also show lower morphogrical 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*) (95, 96). Cystadenomas of the ovary are benign tumors, which are able to, in some cases, undergo the malignant transformation into borderline malignancy tumors, and sometimes even into the cancer (*cystadenocarcinoma*) (97, 98).

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 yrs), who being carriers of at least one of the above-mentioned molecular changes have over twice increased risk of the development of ovarian borderline malignancy tumors (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 yrs. Early tumor

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

Organ	Examination	Age of beginning (years)	Frequency
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* (homozygota GTC)	mammography	35	every 12 months
CHEK2 (1100delC, IVS2+1G>A, del5395)	self examination	20	every month
	medical palpation	20-25	every 6 months
	USG	25	every 12 months (6 months after mammography)
	mammography + USG	40	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)
	mammography + USG	40	every 12 months

detection and its surgical resection can prevent the development of ovarian cancer. Moreover in 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 between 30-35 yrs, on account of almost 3-fold increased risk of the development of this organ's cancer (OR 2.75; p = 0.03) (98, 99).

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 tumor and *CHEK2* I157T was detected,
- control breast examination by using MRI (once a year) in case of female relatives of patients with the 355T/T variant of the *CYP1B1* gene and with benign ovarian tumor.

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

CONCLUSIONS

Around 14 000 women develop breast or ovarian cancer in Poland every year. Advances in clinical genetics of cancers allow to prevent significant number of these cancers. Additionaly, patients of known genetic background may be more effectively diagnosed and treated because of applaying special distinct from standard systems of control examinations and treatment.

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