Risk-adapted approach to prostate cancer screening

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Mass prostatic specific antigen (PSA) testing (population-based PSA screening) has remained controversial, nevertheless there are men cohorts likely to benefit from PSA screening. Heritable factors contribute to 60 % risk for developing familial prostate cancer. Despite the fact that its clinical application is challenging due to polygenic inheritance, advances in new generation sequencing technologies permit identifying highly penetrant germline mutations in genes BRCA1, BRCA2, CHEK2, HOXB13 and MMR associated with tremendous increase in risk of developing the prostate cancer. Several germline mutations are associated with clinically aggressiveness of disease and shortened survival. Targeted screening that is based on family history and genomic aberrations should be the next step towards the precision medicine. Men at elevated risk should been performed for early detection are those with familiar history of prostate cancer, or BRCA1, BRCA2, CHEK2, HOXB13 and MMR pathogenic germline mutation carriers, or first line relatives diagnosed with certain types of cancer. Systematic PSA testing in 1–2 years among germline mutation carriers men beginning at age 45 years would contribute to increase in early detection of localized prostate cancer resulting in more chance of curative treatment and improve survival rates

Key words: *prostate cancer, family history, germline mutation, BRCA1, BRCA2, HOXB13, CHEK2, Lynch syndrome, targeted screening*

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Background

Prostate cancer (PCa) is the most frequently diagnosed malignancy in men and the third leading cause of cancer deaths in developed countries [1–3]. Approximately 60% of all prostate cancers are diagnosed in men aged 65–74 years and only 0.6% of cases are found in men under 44 years of age [4]. Over the last several years, there has been a growing incidence of PCa in Russia due to early detection of localized forms. In 2017, the proportion of individuals with stage I–II PCa among newly diagnosed patients reached 57.0% compared to 40.3% in 2007 [5]. PCa has the highest rate of annual increase in mortality. Despite a significant decrease (by 12.9 %) in the standardized death rate from all cancer types in 2006–2016, PCa mortality has increased by 18.97% [6].

The majority of patients diagnosed with early-stage PCa have indolent disease with a low risk of progression, even without treatment. Two large randomized clinical trials ProtecT (n = 1643; 10 years of follow-up) and PIVOT (n = 731; 19.5 years of follow-up) demonstrated no significant differences in the long-term outcomes between patients with low- to intermediate-risk localized PCa receiving radical treatment (radical prostatectomy or radiotherapy) and those from the active-monitoring group [7, 8].

However, some early-stage tumors can be clinically aggressive and cause rapid disease progression. Patrikidou et al. found that 44% of PCa deaths occur due to progression of primary localized tumors to metastatic disease after radical treatment with a median overall survival of 8.8 months [9]. Of note, 26% of patients developed well-differentiated PCa (Gleason score 6) [9], usually classified as low-risk in the case of prostate-specific antigen (PSA) level of < 10 ng/mL and stage T2a tumor.

The system for risk stratification is still being developed: tumor grading and staging have been changed in the latest TNM classification system (8th edition) [10]; researchers discuss the possibility of dividing intermediate-risk patients into cohorts with favorable and unfavorable prognosis [11, 12] and the need for implementing biomarker assays into routine practice, including genomic [13] and proteomic [14] biomarkers. The strategy for early diagnosis of PCa should be very precise, since the risk of developing this disease varies in different patient groups.

Family history of PCa

Eeles et al. identified the following most significant risk factors for PCa: family history, age, race, lifestyle, and environmental impact [15].

A meta-analysis of 33 studies has demonstrated that history of PCa in first-degree family members (brothers, father, sons) is associated with an increased risk of the disease (rate ratio (RR) 2.48; 95% confidence interval (CI) 2.25–2.74) compared to the general population [16]. The risk was higher in men, whose brothers had a history of PCa (RR 3.14; 95% CI 2.37–4.15) than in those with affected father (RR 2.35; 95% CI 2.02–2.72). Men with two or

more affected first-degree family members were 4.39 times (95% CI 2.61–7.39) more likely to develop the disease. First-degree family history appeared to increase the risk of PCa more in men under 65 (RR 2.87; 95% CI 2.21-3.74), than in men aged 65 and older (RR 1.92; 95% CI 1.49-2.47), p=0.002. A family history of breast or ovarian cancer in a mother or sister was associated with a doubled risk of PCa (RR 2.0; 95% CI 1.0–4.1). Men with a family history of both prostate and breast/ovarian cancer were 5.8 times (95% CI 2.4–14) more likely to develop the disease [17]. However, the impact of family history can be associated with both predisposition and environmental/behavioral factors, such as smoking [18], insolation [19], etc. [20]

Hereditary factors are associated with a 60% increased risk of familial PCa. The Nordic Twin Study of Cancer involving more than 203,000 twins with a median follow-up time of 32 years has demonstrated a 57% heritability of PCa, which was similar to those of skin melanoma, but significantly higher than heritability of other cancers [21]. Significant heritability was observed for non-melanoma skin cancer (43%), ovarian cancer (39%), kidney cancer (38%), breast cancer (31%), and uterine corpus cancer (27%). However, polygenic inheritance of cancer remains a significant obstacle preventing the implementation of these techniques into routine practice [22]. Genome-wide association studies (GWAS) in humans have revealed more than 100 single-nucleotide polymorphisms (SNP) located in various genes and loci and associated with susceptibility to PCa (polygenic inheritance) [23]. Despite a relatively weak effect of each particular SNP (RR 1.1–1.3), cumulatively, several SNPs could increase the risk by 4.6 fold [24]. Moreover, it is extremely important to detect rare highly penetrant mutations associated with an increased risk of PCa or more aggressive course of the disease.

Germline mutations in the *HOXB13* gene

Carriers of the *HOXB13* 251G/A (G84E, rs138213197) germline mutation were found to have the highest risk of developing PCa. The *HOXB13* transcript is involved in the androgen receptor (AR) signaling pathway: it interacts with ARs and regulates transcription of androgen-dependent genes by interacting with a DNA-binding domain of an AR transcription factor (FOXA1); it also promotes androgen-independent growth of PCa cells [25, 26].

M. Ewing et al. screened more than 200 genes in the 17q21-22 region in 5083 patients with PCa and 1401 healthy controls and found that carriers of the *HOXB13* G84E allele are 20.1 times more likely to develop PCa (95% CI 3.5–803.3; $p = 8.5 \times 10^{-7}$) than men in the general population [27]. The frequency of this mutation in patients with PCa reached 1.4% with the highest rates among men with a positive family history (2.2%), early diagnosis (≤ 55 years of age) (2.2%), or both (3.1%) (p = 0.004). However, even men in whom PCa was diagnosed after the age of 55 years and who did not have a family history still demonstrated higher prevalence of this mutation (0.65 %; RR 8.7; 95% CI 1.2–381.3; p = 0.02) compared to healthy individuals (0.1%). Multiple studies conducted in different countries have confirmed that the G84E mutation significantly increases the risk of PCa (RR 1.99–14.70) (Table 1). Beebe-Dimmer et al. demonstrated an increased risk of leukemia in patients with G84E mutation (RR 3.17; 95% CI 1.35–6.03; p = 0.01) and a trend towards an increased risk of bladder cancer in these patients (RR 1.99; 95% CI 0.84–3.86; p = 0.06) [28].

Positive family history of PCa is associated with a higher probability of carrying this mutation (4.31% vs 0.34%; p = 0.002) [29]. One of population studies has shown that carriers of the G84E mutation were more likely to have aggressive forms of PCa: the association appeared stronger for poorly differentiated tumors compared to well-differentiated ones (RR 4.13; 95% CI 1.38–12.38 vs RR 2.71; 95% 0.88–8.30) and for distant disease compared to local disease (RR 4.47; 95% CI 1.28–15.57 vs RR 2.98; 95% CI 1.04–8.49) [30]. However, these differences failed to reach statistical significance and were not confirmed by other studies. Nonetheless, *HOXB13* overexpression in PCa tissue was found to be an independent predictor of early PSA recurrence after radical prostatectomy (p < 0.0001), more advanced disease stages, presence of poorly differentiated tumors, and metastatic lesions in regional lymph nodes (p < 0.0001) [31].

The International Consortium for Prostate Cancer Genetics (ICPCG) has reported the presence of the G84E mutation in 4.6% of families with a history of PCa, primarily in families from Finland (22.4%), Sweden (8.2%), North America (6.1%), and Australia (2.6%) [32]. Later, high prevalence of this mutation and its association with an increased risk of PCa were shown in other countries (Poland [33] and the United Kingdom [34]). The G84E mutation is found only in people of European descent; however recent studies have revealed nonsense germline mutations in the *HOXB13* gene in PCa patients of non-European ancestry (G135E in Chinese men [35], F127C and G132E in Japanese men [36], G216 and R229G in African American men [27], and F240L, A128D, and 96T>A in Portuguese men [37]). Molecular heterogeneity in the *HOXB13* gene confers an increased risk of PCa regardless of geographical factors and ethnicity.

Germline mutations in the *BRCA1* and *BRCA2* genes

Large population studies have demonstrated that *BRCA1* and *BRCA2* gene mutations, associated with hereditary breast and ovarian cancer syndrome (HBOC), [38] can be also found in patients with PCa with a frequency of 2.3% and 0.45% respectively, whereas in the general population, their prevalence does not exceed 0.2%–0.3%. Men carrying mutated *BRCA1* and *BRCA2* genes are at higher risk of developing PCa than men in the general population (RR 2.5–8.6 for the *BRCA2* gene munitions and RR 1.82–3.75

Таблица 1. *Распространенность герминальной мутации G84E (rs138213197) в гене HOXB13 по данным популяционных и центровых исследований*

Table 1. *Prevalence of the G84E germline mutation (rs138213197) in the HOXB13 gene based on populational and single and multicenter studies*

Исследование Study	Тип исследования Study type	Страна Country	Популяция Population	Когорта Cohort		Возраст на момент выявления РПЖ, лет Age at PC diagnosis, years	Частота встречаемости носительства мутации у больных РПЖ, % Frequency of the mutation in patients with PC, %	Увеличение вероятности развития РПЖ при наличии мутации, относительный риск, 95 % доверительный интервал Increased probability of PC for the mutation, relative risk, 95 % confidence interval	*p*	Частота встречаемости носительства мутации в популяции, % Incidence of the mutation in the population, %
				больные РПЖ Patients with PC	мужчины без РПЖ men without PC					
M.R. Akbari и соавт., 2012 [42]	Многоцентровое Multicenter	Канада Canada	Разные Various	1843	2225	59,4	0,7	5,8 (1,3–26,5)	<0,01	0,1
F. Albitar и соавт., 2015 [43]	Моноцентровое Single center	США USA	Европеоидная Caucasian race	232	110	н/д n/a	0,9	0,95 (0,09–10,6)	0,97	0,9
J.L. Beebe-Dimmer, 2015 [28]	Многоцентровое Multicenter	США USA	Европеоидная Caucasian race	42	7218	н/д n/a	1,4	1,99 (1,37–2,90)	<0,0001	0,4
J.P. Breyer и соавт., 2012 [44]	Моноцентровое Single center	США USA	Разные Various	928	930	53,4	1,5 (1,9*, 2,7**)	7,9 (1,8–34,5)	0,0062	н/д n/a
Z. Chen и соавт., 2013 [29]	Многоцентровое (в рамках КИ REDUCE) Multicenter (part of the REDUCE CT)	Разные страны Different countries	Разные Various	20	3887	н/д n/a	0,99 (4,31*)	2,45 (1,48–4,07)	0,01	0,24
H. Chen и соавт., 2018 [45]	Популяционное Population	Норвегия Norway	Европеоидная Caucasian race	779	4738	60,5	2,3	3,8	0,0001	0,7
C.M. Ewing и соавт., 2012 [27]	Многоцентровое Multicenter	США USA	Европеоидная Caucasian race	5083	2662	52,6	1,4	20,1 (3,5–803,3)	$8,5 \times 10^{-7}$	0,07
J. Gudmundsson и соавт., 2012 [46]	Моноцентровое Single center	США USA	Европеоидная Caucasian race	1982	1260	58,3	н/д n/a	14,70 (3,59–60,14)	$1,8 \times 10^{-4}$	н/д n/a
	Моноцентровое Single center	Исландия Iceland	Европеоидная Caucasian race	4537	5444	66,2	н/д n/a	3,67 (1,71–7,90)	$8,8 \times 10^{-4}$	н/д n/a
	Популяционное Population	Нидерланды Netherlands	Европеоидная Caucasian race	1520	1916	63,9	н/д n/a	7,51 (3,99–14,11)	$3,9 \times 10^{-10}$	н/д n/a

Продолжение табл. 1
Continuationof table 1

Исследование Study	Тип исследования Study type	Страна Country	Популяция Population	Когорта Cohort: больные РПЖ Patients with PC	Когорта Cohort: мужчины без РПЖ men without PC	Возраст на момент выявления РПЖ, лет Age at PC diagnosis, years	Частота встречаемости носительства мутации у больных РПЖ, % Frequency of the mutation in patients with PC, %	Увеличение вероятности развития РПЖ при наличии мутации, относительный риск, 95 % доверительный интервал Increased probability of PC for the mutation, relative risk, 95 % confidence interval	*p*	Частота встречаемости носительства мутации в популяции, % Incidence of the mutation in the population, %
J. Gudmundsson и соавт., 2012 [46]	Моноцентровое Single center	Испания Spain	Европеоидная Caucasian race	716	1692	н/д n/a	Не обнаружена Not detected	Недостоверна Insignificant	0,30	н/д n/a
	Моноцентровое Single center	Великобритания United Kingdom	Европеоидная Caucasian race	511	1825	61,7	н/д n/a	14,44 (4,74–44,03)	$2,7 \times 10^{-6}$	н/д n/a
	Моноцентровое Single center	Румыния Romania	Европеоидная Caucasian race	722	857	69,4	н/д n/a	1,19 (0,07–19,0)	1	н/д n/a
R. Karlsson и соавт., 2014 [47]	Популяционное (CAPS) Population (CAPS)	Швеция Sweden	Европеоидная Caucasian race	2805	1709	н/д n/a	4,6	3,4 (2,2–5,4)	$6,4 \times 10^{-10}$	1,3
	Популяционное (Stockholm-1) Population (Stockholm-1)	Швеция Sweden	Европеоидная Caucasian race	2098	2880	н/д n/a	4,3	3,5 (2,4–5,2)	$2,0 \times 10^{-11}$	
W. Kluzniak и соавт., 2013 [33]	Популяционное Population	Польша Poland	Европеоидная Caucasian race	3515	2604	67,3	0,6 (1,0*)	5,00 (1,5–16,7) 8,4 (1,9–37,7)*	0,008 (0,005)*	0,1
Z. Kote-Jarai и соавт., 2015 [34]	Многоцентровое (в рамках КИ ProtecT и проекта UK-GPCSC) Multicenter (part of the ProtecT CT and the UK-GPCSC project)	Великобритания United Kingdom	Европеоидная Caucasian race	8652	5252	н/д n/a	1,5	2,94 (1,94–4,59) 4,53 (2,86–7,34)*	$6,27 \times 10^{-8}$ ($3,1 \times 10^{-8}$)*	0,5
V.H. Laitinen и соавт., 2013 [48]	Популяционное Population	Финляндия Findland	Европеоидная Caucasian race	4571	923	≤55	3,5 (8,4*)	8,8 (4,9–15,7)	$2,3 \times 10^{-18}$	0,5 (1 – при семейном анамнезе) 0.5 (1 for family medical history)
R.J. MacInnis и соавт., 2013 [49]	Популяционное Population	Австралия Australia	Европеоидная Caucasian race	1384	22	52,7	1,4	Частота 16,4 (2,5–107,2) Incidence 16.4 (2.5–107.2)		н/д n/a

Окончание табл. 1
End of table 1

Исследование Study	Тип исследования Study type	Страна Country	Популяция Population	Когорта Cohort: больные РПЖ Patients with PC	Когорта Cohort: мужчины без РПЖ men without PC	Возраст на момент выявления РПЖ, лет Age at PC diagnosis, years	Частота встречаемости носительства мутации у больных РПЖ, % Frequency of the mutation in patients with PC, %	Увеличение вероятности развития РПЖ при наличии мутации, относительный риск, 95 % доверительный интервал Increased probability of PC for the mutation, relative risk, 95 % confidence interval	*p*	Частота встречаемости носительства мутации в популяции, % Incidence of the mutation in the population, %
T.M. Storebjerg и соавт., 2016 [50]	Моноцентровое Single center	Дания Denmark	Европеоидная Caucasian race	995	1622	61,7	2,51	5,12 (2,26–13,38)	$1,3 \times 10^{-5}$	0,49
M. Stott-Miller, 2013 [30]	Популяционное Population	США USA	Европеоидная Caucasian race	1457	1442	н/д n/a	1,3	3,60 (1,21–8,96)	0,01	0,4
J.S. Witte и соавт., 2013 [51]	Семейное + мультицентровое Family + multicenter	США, европейские страны USA, European countries	Разные Various	1645	1019	н/д n/a	1,34 (2,30***)	4,86 (3,18–7,69) 8,41 (5,27–13,76)***	$3,5 \times 10^{-17}$ ($2,7 \times 10^{-22}$ – для возраста ≤55 лет)	0,28
J. Xu, 2013 (ICPCG) [32]	Семейное Family	Финляндия, Швеция, Великобритания, Германия, Франция, США, Австралия Finland, Sweden, United Kingdom, Germany, France, USA, Australia	Разные Various	6422	3705	62,8	5,0	4,42 (2,56–7,64)	$9,9 \times 10^{-8}$	н/д n/a

**При положительном семейном анамнезе. **При анамнезе РПЖ ≥3 родственников. ***При выявлении заболевания в возрасте ≤55 лет.*
**For positive family history. **For PC history in ≥ 3 relatives. ***For the disease diagnosis at ≤ 55 years.*

Примечание. *РПЖ – рак предстательной железы; КИ – клинические исследования; REDUCE – Reduction by Dutasteride of Prostate Cancer Events; CAPS – Cancer of the Prostate in Sweden; ICPCG – International Consortium for Prostate Cancer Genetics; ProtecT – Prostate testing for cancer and Treatment; UK-GPCSC – the UK Genetic Prostate Cancer Study; н/д – нет данных.*
Note. *PC — prostate cancer; CT – clinical trial; REDUCE – Reduction by Dutasteride of Prostate Cancer Events; CAPS – Cancer of the Prostate in Sweden; ICPCG – International Consortium for Prostate Cancer Genetics; ProtecT – Prostate testing for cancer and Treatment; UK-GPCSC – the UK Genetic Prostate Cancer Study; n/a – not available.*

for the *BRCA1* gene mutations in men under 65 years of age) [39, 40]. The most common inherited mutations are 185delAG, 4153delA, and 5382insC in the *BRCA1* gene and 6174delE in the *BRCA2* gene.

A large study by Castro et al. involving 2019 individuals with PCa has shown that *BRCA1/2* mutations confer a more aggressive PCa phenotype with poor survival outcomes [41]. Median age at diagnosis was similar in both carriers and non-carriers of *BRCA1/2* mutations (58 years vs 57 years; p = 0.14), and no differences were seen in their median PSA levels (11.5 vs 11.3 ng/mL; p = 0.93). Poorly differentiated tumors (Gleason score ≥ 8) were twice as common in BRCA1/2 carriers as in non-carriers (35% vs 15%; p = 0.00003). Moreover, patients with mutated *BRCA1/2* genes were more likely to have advanced disease (stage T3–T4) (37% vs 28 %; p = 0.003), regional lymph node metastasis (15% vs 5%; p = 0.00005), and distant metastasis (18% vs 9%; p = 0.005) compared to non-carriers at diagnosis. In patients with localized PCa, the five-year cancer-specific survival (CSS) and metastasis-free survival (MFS) were significantly higher in non-carriers than in those who carried *BRCA1/2* mutations (96% vs 82%; (hazard ratio) HR = 2.6; P = 0.01 and 93% vs 77%; HR = 2.7; P = 0.009, respectively). However, there was no significant difference in survival outcomes between *BRCA1* and *BRCA2* mutation carriers (p = 0.28 and p = 0.29 respectively). Median overall survival (OS) in non-carriers was superior to that in carriers (12.9 vs 8.1 years; HR = 1.9; p = 0.012).

The *BRCA1/2* mutation status may have an impact on long-term outcomes of radical treatment in patients with localized and locally advanced prostate cancer. E. Castro et al analyzed treatment outcomes of 1302 PCa patients and found that 10-year CSS rates were remarkably lower in carriers than in non-carriers (61% vs 85%; HR 2.17; 95% CI 1.16–4.07; p = 0.016). Individuals harboring *BRCA1/2* mutations also demonstrated lower MFS rates compared to those carrying wild-type alleles (50% vs 84%; HR 2.36; 95% CI 1.38–4.03; p = 0.002) [52].

A large multicenter study by Pritchard et al., involving 692 men with PCa, has demonstrated that the prevalence of *BRCA1/2* mutations is higher in patients with metastatic disease than in patients with localized cancer (6.2% vs 4.6% according to the Cancer Genome Atlas (TCGA)), including those with low-to-intermediate–risk tumors (odds ratio (OR) = 5.3, p < 0.001) and high-risk tumors (OR = 2.2; p = 0.002) [53]. There was no association between the presence of germline mutations in the *BRCA1/2* genes and family history of PCa in first-degree family members (p = 1.0), race (p = 0.84), and the age at diagnosis of < 60 years (p = 0.90). Carriers of *BRCA1/2* mutation were more likely to have first-degree relatives with malignancies other than PCa (71% vs 50%; OR 2.4; 95% CI 1.4–4.3; p = 0.001). Inspection of their pedigree information revealed affected relatives with breast cancer (24 probands), ovarian cancer (10), leukemia and lymphoma (10), pancreatic cancer (7), or other gastrointestinal cancers (18).

Full-exome transcriptome sequencing of PCa biopsy specimens (n = 150) demonstrated that 19.3% of all patients with castration-resistant PCa have mutations in DNA repair genes, including *BRCA1*, *BRCA2*, and *ATM*. Clinically significant germline mutations were found in 8% of patients with no somatic genetic alterations in the androgen receptor signaling pathway (*AR*, *FOXA1*), *TP53, PTEN*, and other genes. *BRCA2* gene mutation were the most common germline mutations in patients with castration-resistant PCa.

Germline mutations in the *CHEK2* gene

Like *BRCA* genes, *CHEK2* is a tumor suppressor gene that encodes a protein involved in DNA repair (through initiating cell cycle arrest and p53 stabilization) and activation of the BRCA1 protein. Mutations in the *CHEK2* gene have been linked to familial breast cancer. In the Russian population, the most common *CHEK2* germline mutations are 1100delC, del5395, I157T, and IVS2+1G>A; each of these mutations is associated with carcinogenesis.

The Copenhagen General Population Study examined 86,975 individuals and demonstrated that carriers of the 1100delC mutation are 1.6 times more likely to develop PCa than non-carriers (95% CI 1.0–2.56), although this risk is lower than that for stomach cancer (HR 5.76), kidney cancer (HR 3.61), and sarcoma (HR 3.45) [55].

The pooled results of 5 studies examining *CHEK2**1100delC heterozygosity and risk of cancer in 6,228 PCa cases and 9,258 male controls have shown that *CHEK2* *1100delC was identified in 0.7% of sporadic PCa cases, 1.2% of familial PCa cases, and 0.36% of healthy controls [56] (Table 2). Pooled odds ratios of PCa for *CHEK2* *1100delC heterozygote was 1.98 (95% CI 1.23–3.18) for unselected cases and 3.39 (95% CI 1.78–6.47) for familial cases versus non-carriers (Table 2). A meta-analysis of 8 studies demonstrated that the *CHEK2* 1100delC mutation was associated with higher risk of PCa (OR 3.29; 95% CI 1.85–5.85), although this mutation was irrelevant to familial aggregation phenomenon of PCa (OR 1.59; 95% CI 0.79–3.20; p = 0.20) [57]. Moreover, this meta-analysis confirmed an association between the I157T missense mutation and PCa (OR 1.80; 95% CI 1.51–2.14) and demonstrated a trend towards an increased risk of the disease in patients harboring the IVS2+1G>A mutation (OR 1.59; 95% CI 0.93–2.71; p = 0.09).

The *CHEK2* gene polymorphism may be associated with lethal PCa. A large international study of 703 lethal PCa patients and 1,455 patients with low-risk localized PCa of various origin (USA, China) demonstrated that the frequency of germline *CHEK2* mutations was higher in lethal PCa patients (16 out of 703; 2.28%) than in low-risk PCa patients (24 out of 1455; 1.65%); however, the difference was statistically insignificant (p = 0.31). The 1100delC

Таблица 2. *Герминальные мутации в высокопенетрантных генах, ассоциированные с риском развития рака предстательной железы*
Table 2. *Germline mutations in the high penetrance genes associated with prostate cancer risk*

Ген Gen	Расположение локусов Locus location	Генетические варианты Genetic variants	Частота встречаемости носительства мутации у больных РПЖ, % Incidence of the mutation in patients with PC, %	Увеличение вероятности развития РПЖ при наличии мутации, относительный риск Increased probability of PC for the mutation, relative risk
BRCA1	17q21	185delAG 4153delA 5382insC	0,45 (0,9 – мРПЖ) 0.45 (0.9 for mPC)	1,82–3,75
BRCA2	13q13.1	6174delT	2,3 (5,3 – при мРПЖ) 2.3 (5.3 for mPC)	2,5–8,6 (7,8–23 у мужчин моложе 55 лет) 2.5–8.6 (7.8–23 in males under 55)
CHEK2	22q12.1	1100delC	0,7 (1,9 – при мРПЖ) 0.7 (1.9 for mPC)	1,98–3,29
HOXB13	17q21–22	G84E	1,4*	1,99–20,1

**Мутация G84E в гене HOXB13 обнаруживается только у представителей европеоидной расы.*
**The G84E mutation in the HOXB13 gene is detected only in Caucasians.*

Примечание. *РПЖ – рак предстательной железы; мРПЖ – метастатический рак предстательной железы.*
Note. *PC — prostate cancer; mPC – metastatic prostate cancer.*

mutation demonstrated a significantly higher carrier rate in lethal PCa patients (1.28%) than in low-risk PCa patients (0.16%) of European American origin (OR 7.86; p = 0.0038).

Lynch syndrome

Mutations in DNA mismatch repair genes (*MMR*) are rare germline mutations associated with Lynch syndrome. Mutation in 4 *MMR* genes, including *MLH1, MSH2, MSH6*, and PMS2 were found to be significant for the disease. The cumulative frequency of mutations in MMR genes in the general population has been estimated to be approximately 1:3,100 to 1:370. Patients with Lynch syndrome are more likely to develop PCa (meta-analysis of 12 studies: OR 2.28; 95% CI 1.37–3.29); however, the risk varies significantly between various populations: from 2.5 (95% CI 1.4–4.0; data form German and Danish registers; 2,118 *MMR* gene mutation carriers) to 10.41 (95% CI 2.8–26.65; data from Manchester register; 821 men with Lynch syndrome) [59].

The analysis of cancer histories in 198 families with Lynch syndrome (4,127 men) demonstrated that the cumulative risk of PCa detection in this population was 6.30% (95% CI 2.47–9.96) by 60 years of age and 30% (95% CI 16.54–41.30) by 80 years of age, whereas in the general population, the risk of developing PCa was 2.59% and 17.84% by 60 and 80 years respectively (reported in SEER) [60]. Median age at prostate cancer diagnosis was 65 years (range: 38–89 years) and 11.53% of patients were diagnosed with PCa at age younger than age 50 years. An association between Lynch syndrome and an increased risk of PCa was observed in all age groups (HR 1.99; 95% CI 1.31–3.03; p = 0.0013) with a slightly higher HR in patients under 60 years of age (HR 2.48; 95% CI 1.34–4.59; p = 0.0038). PCa was most frequently diagnosed in carriers of *MSH2* germline mutations, whereas carriers of *MLH1* and *MSH6* mutations were less likely to have PCa. Researchers from Ohio state University examined 188 men with Lynch syndrome and found that *MMR* gene mutations were associated with an increased risk of PCa (RR 4.87; 95% CI 2.43–8.71). The median age at diagnosis was 64 years [61]. However, patients with *MMR* gene mutations did not appear to have earlier onset or a more aggressive phenotype.

An observational multicentre study Prospective Lynch Syndrome Database involving 3,119 patients with Lynch syndrome demonstrated the cumulative incidences of PCa at 75 years of 32 % in *MSH2* gene mutation carriers, 17% in *MLH1* gene mutation carriers, and 18% in *MSH6* gene mutation carriers. The overall 5-year survival for PCa was 100% [62].

Discussion

Serum PSA testing is a standard laboratory method for PCa diagnostics. An elevated PSA level is an indication for prostate biopsy and pathomorphological examination. However, the benefits of PSA testing in the entire male population (population-based PSA screening) are ambiguous, because the largest screening studies demonstrated controversial results. The European Randomized Study of Screening for Prostate Cancer (ERSPC) (n = 162,388) showed reduced prostate cancer-specific mortality after 11 years of follow-up (HR 0.79; 95% CI

Таблица 3. *Злокачественные новообразования, ассоциированные с носительством герминальных мутаций*
Table 3. *Malignant tumors associated with germline mutations*

Злокачественное новообразование Malignant tumor	*BRCA1*	*BRCA2*	*CHEK2*	*MMR*	*HOXB13*
Рак предстательной железы Prostate cancer	+	+	+	+	+
Рак молочной железы Breast cancer	+	+	+	–	–
Рак яичников Ovarian cancer	+	+	+	–	–
Рак толстой кишки Colon cancer	+	–	+	+	–
Рак поджелудочной железы Pancreatic cancer	+	+	–	+	–
Меланома Melanoma	–	+	–	–	–
Рак щитовидной железы Thyroid cancer	–	–	+	–	–
Лейкоз Leukemia	–	–	–	–	+

0.68–0.91), whereas the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (n = 76,685) reported no benefits for cancer-specific mortality even after 13 years of follow-up (HR 1.09; 95% 0.87–1.36). The Cochrane review of 5 randomized studies involving more than 341,000 males demonstrated an association between PSA-screening and increased PCa detection rate (RR 1.3; 95% CI 1.02–1.65), including localized PCa (HR 1.79; 95% CI 1.19–2.70). However, it failed to identify any effect of PSA-screening on both cancer-specific (RR 1.00; 95% CI 0.86–1.17) and overall survival (RR 1.00; 95% CI 0.96–1.03). In 2012, the U.S. Preventive Services Task Force (USPSTF) and then other organizations in Europe and USA recommended against PSA-based screening for PCa in their guidelines. In 2017, the USPSTF updated the guidelines and recommended informing men aged 55-69 years on potential advantages and disadvantages of PSA screening. A patient should be warned about the non-specificity of PSA and the impact of infectious and inflammatory diseases of the prostate, ejaculation, injury, and other factors that can potentially increase the level of this biomarker.

Some categories of men may benefit from PCa screening. Analyzing the subgroup of men with a family history of PCa (7.4%) in the PLCO study, Liss et al. found that they had a significantly higher incidence of PCa (16.9% vs 10.8%; p < 0.01) and higher cancer-specific mortality (0.56 % vs 0.37%; p < 0.01) [63]. Of note, the age at diagnosis, baseline PSA level, and Gleason score were similar in patients with both positive and negative family history. Multivariable analysis showed that screening in men with a positive family history (including routing PSA testing) was associated with a trend toward decreased cancer-specific mortality (HR 0.49; 95% CI 0.22-1.1; p = 0.08). Current guidelines of the National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) consider men over 45 years of age with a positive family history as a high-risk group, which should undergo screening for early detection of PCa (level of evidence 2a in NCCN and 2b in EAU).

Today, there is no doubt that positive family history of PCa and other cancers is a significant risk factor for PCa development (Table 3). Careful family history taking and identification of close relatives affected by cancer should become a routine practice for physicians. Particular attention should be paid to the presence of 2 or more relatives with a history of cancer, cases of early PCa (< 55 years), and early breast or ovarian cancer (< 50 years).

In addition to family history, certain genetic polymorphisms (germline mutations in high-penetration genes) may significantly increase the risk of PCa and are often associated with earlier onset. Carrying of *BRCA1, BRCA2*, and *CHEK2* (for Caucasian race) gene mutations is associated with more aggressive disease and poorer survival. Other mutations are either disease-specific (in the HOXB13 gene) or attributed to hereditary syndromes (*MMR* gene mutations in Lynch syndrome). These mutations increase the risk of early disease onset. Men diagnosed with these

mutations should undergo regular PSA testing once a year or once every two years from the age of 45 years.

If no genetic testing is planned, a doctor shall pay particular attention to family history and presence of 1 or more relatives with one of the following diseases: breast cancer, ovarian cancer, pancreatic cancer (suspected carrier of *BRCA2* gene mutations), colon cancer, rectal cancer, uterine cancer, stomach cancer, small bowel cancer, kidney cancer, and tumors in the biliopancreatoduodenal area (suspected Lynch syndrome). However, even a negative family history does not completely exclude germline mutations in the *BRCA2* gene associated with a high risk of lethal outcome.

Russian studies recommend including genetic testing for *BRCA1/2* gene mutations into screening programs for detecting hereditary breast and ovarian cancer [64]. Germline *BRCA1/2* gene mutations were detected in 5.9% of patients with breast cancer and 20.9% of patients with ovarian cancer; the 5382insC mutation was observed in 4.0% and 11.6% of patents with breast and ovarian cancer respectively. High prevalence of germline mutations in the *BRCA1* and *BRCA2* genes among patients with ovarian cancer indicates the need for genetic screening in these women.

The efficacy of targeted PSA screening in men is currently being assessed in a large multicenter international study IMPACT (Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted screening in *BRCA1/2* mutation carriers and controls). The study has recruited 2,481 men aged 40–69 years, including 791 *BRCA1* mutation carriers, 731 *BRCA2* mutation carriers, and 959 controls not harboring *BRCA1/2* mutations with a negative family history [65]. After the first round of screening, the estimated positive predictive value (PPV) of PSA testing was 37.5% in *BRCA1* mutation carriers vs 23.3% in controls and 48.0% in *BRCA2* mutation carriers vs 33.3% in controls. The PPV of PSA testing for detecting aggressive disease (intermediate- and high-risk PCa) was higher in *BRCA2* mutation carriers than in controls (2.38% vs 0.71%; $p = 0.04$). No cases of advanced-stage PCa (N+, M1) were observed in this study. Final results will be published after 5 rounds of screening.

Conclusion

The results of multiple studies suggest high prevalence of germline mutations (in *BRCA1, BRCA2, CHEK2, HOXB13*, and *MMR* genes), the majority of which are associated with an increased risk of PCa, more aggressive disease course, and poorer survival. Early diagnostics should be considered for men at high-risk of developing PCa, including those with familial PCa, carriers of germline mutations in the *BRCA1, BRCA2, CHEK2, HOXB13*, or *MMR* genes, and patients, whose first-degree family members had cancer. Regular PSA testing of men carrying these mutations once every 1 to 2 years starting from the age of 45 will improve the detection of early-stage PCa, enable radical treatment, and increase survival.

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