A personalised approach to prostate cancer screening based on genotyping of risk founder alleles

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Background: To evaluate whether genotyping for 18 prostate cancer founder variants is helpful in identifying high-risk individuals and for determining optimal screening regimens.

Methods: A serum PSA level was measured and a digital rectal examination (DRE) was performed on 2907 unaffected men aged 40–90. Three hundred and twenty-three men with an elevated PSA ($\geqslant 4$ ng ml^{-1}) or an abnormal DRE underwent a prostate biopsy. All men were genotyped for three founder alleles in *BRCA1* (*5382insC, 4153delA* and *C61G*), for four alleles in *CHEK2* (*1100delC, IVS2 + 1G > A, del5395* and *I157T*), for one allele in *NBS1* (*657del5*), for one allele in *HOXB13* (*G84E*), and for nine low-risk single-nucleotide polymorphisms (SNPs).

Results: On the basis of an elevated PSA or an abnormal DRE, prostate cancer was diagnosed in 135 of 2907 men (4.6%). In men with a *CHEK2* missense mutation *I157T*, the cancer detection rate among men with an elevated PSA or an abnormal DRE was much higher (10.2%, $P = 0.0008$). The cancer detection rate rose with the number of SNP risk genotypes observed from 1.2% for men with no variant to 8.6% for men who carried six or more variants ($P = 0.04$). No single variant was helpful on its own in predicting the presence of prostate cancer, however, the combination of all rare mutations and SNPs improved predictive power (area under the curve = 0.59; $P = 0.03$).

Conclusion: These results suggest that testing for germline *CHEK2* mutations improves the ability to predict the presence of prostate cancer in screened men, however, the clinical utility of incorporating DNA variants in the screening process is marginal.

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Inherited factors contribute to the risk of prostate cancer. These factors include a positive family history of cancer and a mutation in one of several prostate cancer susceptibility genes (BRCA2, BRCA1, CHEK2, NBS1, HOXB13) (Struewing et al, 1997; Dong et al, 2003; Cybulski et al, 2004; Kote-Jarai et al, 2011; Ewing et al, 2012; Leongamornlert et al, 2012). A number of genome-wide association studies (GWAS) have confirmed over 70 single-nucleotide polymorphisms (SNPs) to be associated with prostate cancer risk (Amundadottir et al, 2006; Al Olama et al, 2009; Eeles et al, 2009; Gudmundsson et al, 2009; Takata et al, 2010; Haiman et al, 2011; Kote-Jarai et al, 2011; Eeles et al, 2013). The odds ratios for the susceptibility alleles and prostate cancer risk range from about 1.5 (for BRCA1) to about 20 (for HOXB13), but the odds ratios for the SNPs are generally much lower (range 1.1–1.6).

It has been proposed that one of the utilities resulting from the GWAS studies should be our ability to categorise men into various levels of prostate cancer risk, based on their genotypes at a number of associated SNPs (Macinnis et al, 2011; Goh et al, 2012). The various categories could in turn be used to define optimum surveillance strategies for men at various levels of risk. In practical terms, surveillance currently consists of annual digital rectal examination and serum prostate-specific antigen (PSA). A personalised approach to screening implies the initiation of screening at different ages, and possibility at different frequencies, depending on the inherent level of risk. In one optimistic scenario, some men might be identified to have a sufficiently low risk of prostate cancer that they might forego screening altogether, or postpone it until later in life.

In Poland, we have identified nine founder alleles in four susceptibility genes (Cybulski et al, 2013; Kluźniak et al, 2013). Three founder alleles are in BRCA1 (5382insC, 4153delA and C61G), four are in CHEK2 (1100delC, IVS2 + 1G > A, del5395 and I157T) and one (657del5) is in NBS1. We have also confirmed the recently reported association of prostate cancer with HOXB13, although the prevalence of the G84E risk allele is very low (one in 1000 individuals) (Kluźniak et al, 2013). To measure the impact of genotyping men for these genetic variants on the efficiency of prostate cancer screening, we performed PSA and digital rectal examination (DRE) in 2907 men aged 40–90 in Poland. We sought to evaluate whether or not genotyping of 18 different risk alleles in the Polish population will be helpful for determining screening regimens in men with and without a family history of prostate cancer.

MATERIAL AND METHODS

Patients. We enrolled 2907 men, ages 40–90, with no history of prostate cancer or other cancer, between 2009 and 2012. Study subjects were derived from two sources. The first series consisted of men who had been seen in the outpatient department of the International Hereditary Cancer Center in Szczecin between 2002 and 2009. From the clinic records, 2476 men with no personal history of prostate cancer were invited by mail to participate. Men were preferentially invited to participate if they had a positive family history of prostate cancer or if they carried a founder mutation in one of the three susceptibility genes. Of the 2476 invitations sent, 877 men (35.4%) accepted the invitation and consented to participate. Of these, 450 had a positive family history of prostate cancer and 427 had no family history of prostate cancer. Some men had been tested for mutations in BRCA1, CHEK2 and NBS1 (eight alleles). The second series included 2030 men who were part of a population-based survey of 1.5 million residents of West Pomerania, which was designed to identify family cancer clusters in 2002. For the current study, 8410 questionnaires of men were selected, including 2713 questionnaires of men with a family history of prostate cancer and 5688 men (at random) with no

family history. The 8410 men were invited by mail to participate in the study. Of these, 2705 men came to the study center for an interview between 2009 and 2011. Of these, 2030 men (74.5%) accepted the invitation to participate. Eight hundred twenty-eight men had a positive family history and 1202 men had no family history of prostate cancer. A blood sample was taken from all men for PSA level and DNA analyses.

Genotyping. DNA was isolated from 5 to 10 ml of peripheral blood. Nine founder mutations (5382insC, 4153delA, C61G in BRCA1; 1100delC, IVS2 + 1G > A, del5395, I157T in CHEK2; 657del5 in NBS1, and G84E in HOXB13) were detected as described previously (Cybulski et al, 2006; Cybulski et al, 2011; Kluźniak et al, 2013). In brief, they were detected using ASO-PCR, RFLP-PCR, or TaqMan assays.

We also chose nine SNPs for analysis. These SNPs were selected from a panel of 30 candidate SNPs identified by various GWAS studies between 2006 and 2011 (Amundadottir et al, 2006; Al Olama et al, 2009; Eeles et al, 2009; Gudmundsson et al 2009; Kote-Jarai et al, 2011; Haiman et al, 2011). The 30 candidate SNPs were first analysed for association in a series of 661 unselected prostate cancer cases and 720 controls from Poland; 25 of the 30 SNPs were successfully genotyped. The nine SNPs included here were chosen from the 25 SNPs based on the highest odds ratios and the corresponding P-values (Supplementary Table 1). A SNP was chosen, when at least one genotype (homozygous or heterozygous) was associated odds ratio for unselected prostate cancer was 1.4 or higher, or the odds ratio was 0.7 or lower (compared with a common homogenous genotype), and the association was significant with $P < 0.05$. For five of nine selected SNPs P-value was < 0.01, and for four of nine selected SNPs the association was significant with P-value between 0.01 and 0.04. The selected SNPs were genotyped using TaqMan assays in the current series of 2907 men undergoing prostate cancer screening. All nine SNPs were successfully genotyped in 2804 of 2907 men (96.5%).

Study protocol. A serum PSA level was measured for all 2907 men and a DRE was performed on 2878 men by one of the three reference urologists. In the event of an elevated PSA level ($\geqslant 4.0$ ng ml^{-1}) or an abnormal DRE, the man was invited for a 24-core prostate biopsy. Cancer was diagnosed if it was present in any of the 24 cores.

Statistical analysis. We wished to study the impact of 18 alleles on the detection of prostate cancer in 2907 men undergoing prostate cancer screening. We estimated the prevalence of detected-prostate cancer in the study sample as a whole (total cancers detected/total subjects) and among subgroups defined by age, family history of prostate cancer (yes/no and number of affected relatives) and by the variant alleles. The nine SNPs were studied individually and in combination. To study these in combination, a SNP count was constructed for each study subject, ranging from zero to nine, depending on the number of abnormal genotypes detected.

Receiver operating characteristics were constructed to estimate the area under the curve (AUC) under various screening protocols. To evaluate the performance of the genetic markers (rare mutations and/or common SNPs) in predicting prostate cancer detected by PSA screening, AUCs were calculated in a group of men with PSA $\geqslant 4$ ng ml^{-1} ($n = 204$); the AUCs were calculated including DRE, the genetic factors alone and both in combination. The analyses were carried out using MedCalc for Windows, version 9.5.0.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

We screened 2709 Polish men with serum PSA and DRE (Figure 1). In these, 424 men (14.6%) had an abnormal PSA test

or DRE. Three hundred twenty-three of the 424 men (76%) underwent a trans-rectal 24 core ultrasound-guided biopsy (76 men were biopsied because of abnormal PSA and DRE, 132 men were biopsied because of elevated PSA only, and 115 had biopsy because of positive DRE only). In total, prostate cancer was diagnosed in 135 of the 323 (42%) men, corresponding to 4.6 cancers detected per 100 men screened using combination of PSA and DRE.

We analysed the effects of age and family history on the prostate cancer detection rate. As expected, age was a strong predictor of prostate cancer (Table 1). The prevalence of prostate cancer rose steeply with age from 0.5 per 100 men aged 40–50 to 20.5 per 100 for men aged 81–90. A family history of prostate cancer in a first- or second-degree relative was associated with only a modest increase in the cancer detection rate (Table 2). The cancer detection rate rose from 4.0% in men with no affected relative to 5.4% in men with a positive family history ($P = 0.1$). The majority of men with a positive family history had only one affected relative

(89%). Only 22 men (1.7%) could be considered to come from a prostate cancer family (three or more cases of prostate cancer).

We studied the effect of nine rare mutations of BRCA1, NBS1, CHEK2 and HOXB13 on the prostate cancer detection rate. A total 303 of 2907 men (10.4%) had a mutation in one of the susceptibility genes (Table 3). Of the nine rare mutations, only CHEK2 I157T mutation was associated significantly prostate cancer – prostate cancer was detected in 17 of 166 carriers of the I157T allele (10.2%) and it was detected in 118 of 2741 non-carriers (4.3%) (OR = 2.5, P = 0.0008). The other genes were not contributory including the highly penetrant HOXB13.

Among CHEK2 carriers, men in all age groups experienced a cancer detection rate in excess of that of non-carriers (Table 4). Among CHEK2 carriers, the cancer detection rate was higher for men with positive family history than in men with no family history (12.7% vs 8.7%) but this was not statistically significant.

The results of including the nine selected SNPs in the screening evaluation are presented in Table 5. In general, individual
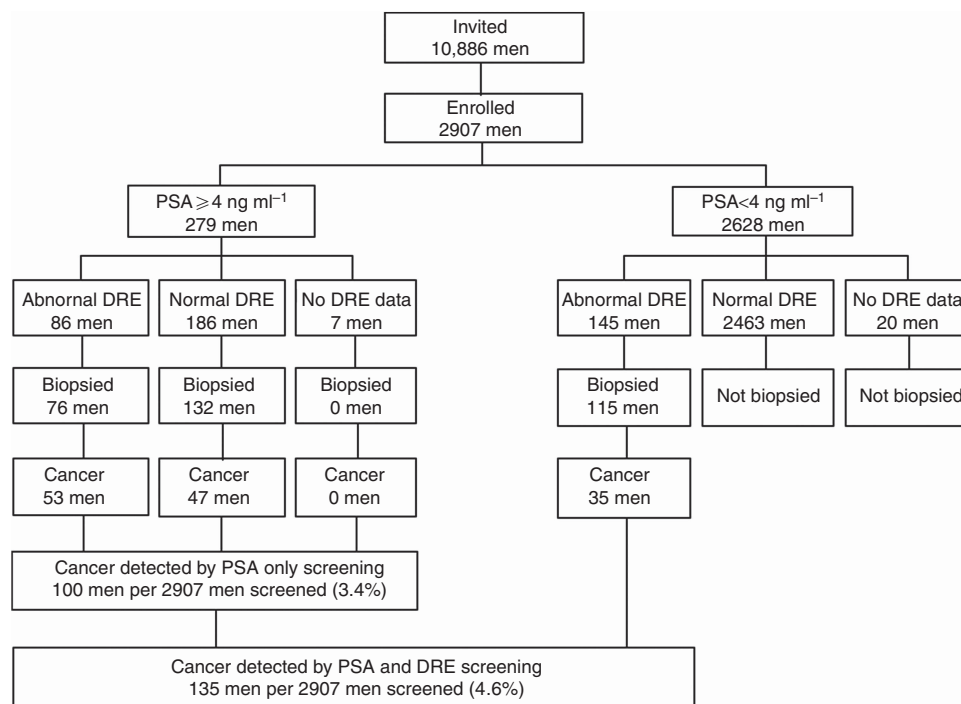

Figure 1. Diagram of the study of the 2907 men who underwent PSA and DRE screening.

Table 1. The frequency of prostate cancer detected in PSA and DRE-based screening and in PSA only screening

Age (years)	No. of men screened	Median PSA	PSA ≥4 ng ml⁻¹, no. (%)	DRE positive, no. (%)	No. of cancers detected (cancer prevalence per 1000)	
					PSA only screening	PSA and DRE screening
40–50	182	0.75	3 (1.6)	9 (4.9)	0 (0)	1 (5)
51–60	1225	0.98	66 (5.4)	67 (5.5)	21 (17)	28 (23)
61–70	1023	1.31	121 (11.8)	92 (9.0)	50 (49)	66 (65)
71–80	438	1.57	82 (18.7)	54 (12.3)	25 (57)	32 (73)
81–90	39	1.68	7 (17.9)	9 (23.1)	4 (102)	8 (205)
Any	2907	1.11	279 (9.6)	231 (7.9)	100 (34)	135 (46)

Abbreviations: DRE = digital rectal examination; PSA = prostate-specific antigen. 'PSA screening only' refers to cancers detected using PSA screening alone (35 cancers diagnosed in DRE-positive men with PSA <4 ng ml⁻¹ are excluded). 'PSA and DRE screening' refers to cancers detected using both PSA and DRE screening (35 cancers diagnosed in DRE-positive men with PSA <4 ng ml⁻¹ are included).

Table 2. Family history of PC and probabilities of cancer risk

	No. of men screened	No. of cancers detected (cancer prevalence per 1000)	
		PSA only screening	PSA and DRE screening
Family history			
Negative	1629	50 (31)	66 (40)
Positive	1278	50 (39)	69 (54)
Number of PCs in relatives			
1	1136	46 (40)	62 (55)
2	120	3 (25)	6 (50)
3+	22	1 (45)	1 (45)

Abbreviations: DRE = digital rectal examination; PC = prostate cancer; PSA = prostate-specific antigen.

Table 3. Number of carriers of mutations in four cancer susceptibility genes and probabilities of cancer detected

Gene	No. of men with mutation	No. of cancers detected (cancer prevalence per 1000)	
		PSA only screening	PSA and DRE screening
BRCA1	57	1 (18)	2 (35)
CHEK2 all	217	14 (64)	19 (88)
CHEK2 truncating	50	1 (20)	2 (40)
CHEK2 I157T	166	13 (78)	17 (102)
NBS1	30	1 (33)	1 (33)
HOXB13	5	0 (0)	0 (0)
Any mutation	303	16 (53)	23 (73)
No mutation	2604	84 (32)	113 (43)

Abbreviations: DRE = digital rectal examination; PSA = prostate-specific antigen.

Table 4. Probability of prostate cancer detected, by age and family history, among CHEK2 I157T carriers

	No. of patients	No. of cancers detected (cancer prevalence per 1000)	
		PSA only screening	PSA and DRE screening
Age interval			
All	166	13 (78)	17 (102)
40–50	14	0 (0)	1 (71)
51–60	68	5 (73)	6 (88)
61–70	61	6 (98)	7 (115)
71–80	20	2 (100)	2 (100)
80–90	3	0 (0)	1 (333)
Positive family history of PC	63	7 (111)	8 (127)
Negative family history of PC	103	6 (58)	9 (87)

Abbreviations: DRE = digital rectal examination; PC = prostate cancer; PSA = prostate-specific antigen.

genotypes for the SNPs did not predict the presence of prostate cancer (Table 5a). One possible exception was rs16901979. The detection rates in men without and with this variant allele were 4.6% and 8.4%, respectively (OR = 1.9; $P = 0.06$). The probability of prostate cancer being detected increased with the number of variant SNP genotypes observed from 1.2% for carriers of no risk genotype to 8.6% for carriers of six or more risk genotypes ($P = 0.04$) (Table 5b). Compared with the cancer detection rate of the population as a whole, men with six or more risk SNP genotypes were observed to be at 1.9-fold elevated risk ($P = 0.3$). Table 5b includes all nine SNPs and Table 5c includes only the five SNPs used to construct the original Zheng model (Zheng et al, 2008).

To evaluate the global performance of the genetic markers, receiver operating characteristics were constructed to estimate the AUC under various screening protocols. We assessed the performance of the genetic variants (in addition to PSA) in men with $PSA \geqslant 4 \, ng \, ml^{-1}$ who underwent a biopsy (Table 6). The AUC for the rare mutations alone was 0.54, the AUC for the nine SNP model was 0.53 and the AUC for the five SNP model was 0.56 (P-values between 0.2 and 0.4). The AUC for the combination of rare mutations and the five SNP model of Zheng was 0.59 and was statistically significant ($P = 0.03$). In addition, we investigated if genetic variants add important information to DRE. The AUC for DRE alone was 0.66, after adding rare mutation and nine SNP data it increased to 0.72 ($P = 0.06$), after adding rare mutation and five SNP data it increased to 0.72, and the difference was significant ($P = 0.03$).

Information on Gleason grade was available for all 135 men with cancer. Overall, 43% of the cases had a Gleason score of 7 or higher. The proportion of men with a high Gleason score was not higher than that for any of the genetically defined subgroups.

DISCUSSION

Prostate cancer is among the leading causes of morbidity and mortality for cancer in men. In the absence of lifestyle interventions or chemoprevention, prevention is based on early detection. In this study, we sought to evaluate the potential benefit of applying a personalised, gene-based approach to prostate cancer prevention; specifically, we ask if genotyping for 18 susceptibility alleles can improve the performance of the PSA test in a population-based setting. In theory, this could be achieved if we could use the susceptibility alleles, singly or in combination, to define a subgroup of men who harboured the majority of cancers. This was not the case; of the 135 men with prostate cancer, only 22 men had a mutation in one of the known genes and only 5 men carried six or more risk SNP genotypes. Furthermore, the impact of a first-degree relative with prostate cancer on cancer detection was small and was not helpful in classifying men. In contrast, the age of the patient was highly predictive of the presence of cancer and was much more informative than any of the genetically defined categories – the prevalence of prostate cancer rose from 0.5 to 21% for men in categories of increasing age.

Table 5. Probabilities of prostate cancer detected by SNPs genotype: (a) for each SNP in isolation; (b) by SNP count – nine SNP model; and (c) by SNP count – five SNP model (Zheng *et al*, 2008).

(a)

SNP	Risk genotype	No. of men	No. of cancers detected (cancer prevalence per 1000)	
			PSA only screening	PSA and DRE screening
rs1859962[a]	GG	827	29 (35)	40 (48)
rs1447295[a]	AA or AC	581	23 (40)	29 (50)
rs6983267[a]	GG	661	27 (41)	34 (51)
rs4430796[a]	AA	865	35 (40)	46 (53)
rs16901979[a]	AA or AC	143	9 (63)	12 (84)
rs17021918	CC	1215	44 (36)	58 (48)
rs11649743	GG	1832	69 (38)	95 (52)
rs7679673	CC	836	28 (34)	41 (49)
rs11228565	AA or AG	940	39 (41)	45 (48)
All men	Any	2907	100 (34)	135 (46)

(b)

No. of risk genotypes	No. of men	%	No. of cancers detected (cancer prevalence per 1000)	
			PSA only screening	PSA and DRE screening
0	85	3.0	1 (12)	1 (12)
1	350	12.5	10 (29)	13 (37)
2	740	26.4	24 (32)	35 (47)
3	832	29.7	29 (35)	43 (52)
4	551	19.6	22 (40)	25 (45)
5	188	6.7	10 (53)	11 (58)
6–8	58	2.1	3 (52)	5 (86)

(c)

No. of risk genotypes	No. of men	%	No. of cancers detected (cancer prevalence per 1000)	
			PSA only screening	PSA and DRE screening
0	298	10.6	9 (30)	13 (44)
1	1084	38.6	37 (34)	51 (47)
2	981	35.0	27 (28)	38 (39)
3	391	13.9	23 (59)	28 (72)
4	49	1.7	3 (61)	3 (61)
5	1	0.04	0 (0)	0 (0)

Abbreviations: DRE = digital rectal examination; PSA = prostate-specific antigen; SNP = single-nucleotide polymorphism.
[a]SNPs from Zheng model (Zheng *et al*, 2008)

Table 6. ROC analysis of the addition of genetic factors (SNPs and/or rare variants) to the prediction of prostate cancer in 208 subjects with PSA ⩾ 4 ng ml^{-1}

Variables	AUC	s.e.	95% CI[a]	*P*-value
Genetic factors				
Nine rare mutations	0.54	0.040	0.47–0.61	0,27
Five SNP model	0.56	0.040	0.49–0.63	0.15
Nine SNP model	0.53	0.040	0.46–0.60	0.42
Nine rare mutations and five SNP model	0.59	0.040	0.52–0.66	0.03
Nine rare mutations and nine SNP model	0.58	0.040	0.50–0.64	0.06
Clinical and genetic factors				
DRE	0.66	0.038	0.59–0.72	<0.0001
DRE and nine rare mutations and five SNPs	0.72	0.036	0.66–0.78	0.03*
DRE and nine rare mutations and nine SNPs	0.72	0.036	0.65–0.78	0.06*

Abbreviations: AUC = area under the curve; CI = confidence interval; DRE = digital rectal examination; ROC = receiver operating characteristic; SNP = single-nucleotide polymorphism. Nine rare mutations – a mutation in *BRCA1*, *CHEK2*, *NBS1* or *HOXB13*. SNP model – a SNP count was constructed for each study subject, ranging from zero to nine for nine SNP model and ranging from zero to five for five SNP model, depending on the number of abnormal genotypes detected; SNPs included in each model are shown in Table 5. *P*-values under null hypothesis: true area = 0.5. *P-value from comparison with AUC for DRE.
[a]Binomial exact.

In this study, the most significant genetic association was seen with the *CHEK2 I157T* allele. This allele is present in 5% of the Polish population and in the current study was associated with a relative risk of 2.5 for the detection of prostate cancer. Cancer detection rates in men without and with this allele were 4.0% and 10.2%, respectively (OR = 2.5; 95% CI 1.5–4.3; *P* = 0.0008). Cancer detection rate was 12.7% for carriers of the *I157T* allele who reported a positive family history of prostate cancer (OR = 3.2; 95% CI 1.5–6.9; *P* = 0.004; compared with non-carriers). Among *CHEK2* carriers, men in all age groups experienced a cancer detection rate in excess of that of non-carriers. Previously, in a

large association study, we reported an odds ratio of 1.8 (95% CI 1.5–2.2) associated with this allele for unselected cases and 2.7 (95% CI 1.7–3.3) for familial cases of prostate cancer (Cybulski *et al*, 2013). The *I157T* allele also was associated with an odds ratio of 1.5 for unselected prostate cancer and 2.1 for familial prostate cancer in Finland (Seppälä *et al*, 2003). The *CHEK2 I157T* mutation has a world-wide distribution. The allele is most common in populations with Northern European origins (Zhang *et al*, 2008).

We did not find the presence of a *BRCA1* mutation to be a predictor of risk, and we do not present data to justify testing men for the three Polish founder alleles (there are no known founder alleles in *BRCA2* in Poland). The role of serum PSA screening in *BRCA1* and *BRCA2* mutation carriers is being evaluated in a large international research study called IMPACT. Preliminary analysis of the data from that support the rationale for continued PSA screening in such men, but do not recommend that all men be screened for mutations (Mitra *et al*, 2011).

The *HOXB13 G84E* mutation is associated with a high relative risk of prostate cancer in several countries, including Poland, but the allele is rare (0.2% of controls) and was not present in any of the 135 detected cases of prostate cancer. In Sweden, this allele is much more common (1.3% of controls) and may be a significant contributor to the burden of prostate cancer in that country (Karlsson *et al*, 2012).

On the basis of the receiver operating characteristics, no variant in isolation was helpful in predicting prostate cancer, but in combination, rare mutations and SNPs were associated with modestly elevated AUC of 0.59 (*P* = 0.03). These results suggest that our selection of genetic variants does not add very much clinically at this stage, and our series the genetic markers do not have clinical utility. However, many more markers have recently become available and therefore a fuller assessment of genetic risk may yet in the future add to existing clinical markers (Eeles *et al*, 2013).

Association studies have identified numerous SNPs associated with prostate cancer, but the clinical role of these SNPs in risk management has not been proven. Klein *et al*, (2012) evaluated 50 previously identified SNPs for predicting prostate cancer in a nested case–control study from a large prospective population-based cohort (943 cases and 2829 matched controls). They found no clinical benefit in the information gained from the SNPs beyond that of PSA alone (of note, the Malmo cohort includes 28 000 men. If this were equivalent to a real clinical situation, it would have meant the genotyping all 28 000 men).

There have been a number of studies evaluating the role of prostate cancer screening in men at elevated risk of the disease based on a family history of prostate cancer (McWhorter *et al*, 1992; Narod *et al*, 1995; Sartor, 1996; Matikainen *et al*, 1999; Bunker *et al*, 2002; Catalona *et al*, 2002; Mäkinen *et al*, 2002; Valeri *et al*, 2002; Uzzo *et al*, 2003; Horsburgh *et al*, 2005; Kiemeney *et al*, 2008). Many authors support screening high-risk men, but the expected benefit of such a programme in a population-based setting has not been formally evaluated previously. In the present study, men were evaluated before screening (i.e., before the discovery of an abnormal PSA or DRE). Most previous studies have focused on men with an abnormal PSA test – in this situation, it is found that the positive predictive values of the PSA test is greater in high-risk groups compared with men at average risk (Catalona *et al*, 2002), but there has been no subgroup identified for which the risk is sufficiently low that a biopsy can be avoided.

There are several limitations to our study. Our study is based in Poland and the results might not be generalisable to other countries with different distributions of susceptibility alleles. For example, there is no founder allele for *BRCA2* in Poland, but these are present in other populations such as Iceland (Thorlacius *et al*, 1997) and Quebec (Ghadirian *et al*, 2009). The *HOXB13 G48E* mutation is much more common in Sweden than in Poland (Karlsson *et al*, 2012). Our study population was nearly 3000 men, but only 135 were found to have prostate cancer and the number of cases in any genetic subgroup was small. We studied two different populations with different sampling strategies to have adequate representation from both the average-risk and high-risk communities (1278 men had a positive family history of prostate cancer and 1629 men had no family history of prostate cancer). Our criteria for biopsy included a single elevated PSA level $\geqslant 4.0 \, \text{ng ml}^{-1}$ or an abnormal DRE. We did not routinely recommend repeat PSA tests or estimate PSA doubling times, because these are not standard screening practices in Poland. We routinely sampled 24 cores, and our sensitivity might have been higher had we taken more core samples or had a less stringent criteria for a biopsy.

Our study does not evaluate the utility of PSA screening *per se* in reducing mortality from prostate cancer, and the benefit of PSA screening in terms of mortality remains unclear. Three large screening studies are evaluating the role of population screening (Schröder and Bangma, 1997; Prorok *et al*, 2000; Donovan *et al*, 2003). The ERSPC study reported a significant reduction in prostate cancer-specific mortality (RR 0.84, 95% CI 0.73–0.95), whereas the PLCO study found no significant benefit (RR 1.15, 95% CI 0.86–1.54). Pooled data from five randomised controlled trials (including the PLCO and ERSPC) currently demonstrate no significant reduction in prostate cancer-specific and overall mortality (Ilic *et al*, 2013). The American Cancer Society currently recommends a discussion about PSA screening with men aged $\geqslant 50$ years, or aged $\geqslant 45$ years for African-American men or those with a family history of prostate cancer (Smith *et al*, 2009). It has been estimated that 84% of screen-detected cancers will not impact on mortality (McGregor *et al*, 1998). This may not necessarily be the case for men with germline mutations in the genes studied here. It is noteworthy that the cancers in men with *BRCA2* mutations and the *NBS1* mutation appear to be particularly aggressive and the benefits of screening for these men may exceed that of the general population (Sigurdsson *et al*, 1997; Narod *et al*, 2008; Mitra *et al*, 2008; Edwards *et al*, 2010; Thorne *et al*, 2011; Kote-Jarai *et al*, 2011; Cybulski *et al*, 2013). Therefore, men with germline mutations may potentially be at risk of developing highly aggressive prostate cancers. It is important that future studies address these questions.

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APPENDIX

Tomasz Byrski, Paulina Sikorska-Radek, Józef Matych, Jacek Wilkosz, Waldemar Różański, Jacek Kiś, Krzysztof Bar, Piotr Słupski, Piotr Jarzemski, Piotr Bryniarski, Andrzej Paradysz, Konrad Jersak, Jerzy Niemirowicz, Michał Skrzypczyk, Jakub Dobruch, Jerzy Świtała, Zbigniew Kwias, Andrzej Borówka, Wenancjusz Domagała, Maria Chosia, Mirosław Kordowski, Joanna Bagińska, Kazimierz Krajka, Sławomir Archimowicz, Marek Szwiec, Marcin Życzkowski, Thierry van de Wetering, Małgorzata Stawicka, Olga Haus, Hanna Janiszewska, Agnieszka Stembalska, Maria Małgorzata Sąsiadek.