Polygenic susceptibility to prostate and breast cancer: implications for personalised screening

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BACKGROUND: We modelled the efficiency of a personalised approach to screening for prostate and breast cancer based on age and polygenic risk-profile compared with the standard approach based on age alone.

METHODS: We compared the number of cases potentially detectable by screening in a population undergoing personalised screening with a population undergoing screening based on age alone. Polygenic disease risk was assumed to have a log-normal relative risk distribution predicted for the currently known prostate or breast cancer susceptibility variants (N = 31 and N = 18, respectively).

RESULTS: Compared with screening men based on age alone (aged 55 – 79: 10-year absolute risk ≥ 2%), personalised screening of men age 45 – 79 at the same risk threshold would result in 16% fewer men being eligible for screening at a cost of 3% fewer screen-detectable cases, but with added benefit of detecting additional cases in younger men at high risk. Similarly, compared with screening women based on age alone (aged 47 – 79: 10-year absolute risk ≥ 2.5%), personalised screening of women age 35 – 79 at the same risk threshold would result in 24% fewer women being eligible for screening at a cost of 14% fewer screen-detectable cases.

CONCLUSION: Personalised screening approach could improve the efficiency of screening programmes. This has potential implications on informing public health policy on cancer screening.

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The benefits of any cancer screening programme may be offset by adverse consequences, such as false-positive findings (positive screening findings that do not result in a diagnosis of cancer), overdiagnosis (diagnosis of a cancer as a result of screening that would not have been diagnosed in a person’s lifetime had screening not taken place) (Paci et al, 2004), and overtreatment. A screening programme becomes viable if it does more good than harm at reasonable cost (Gray et al, 2008).

Prostate and breast cancers are the two most commonly diagnosed cancers in men and women, respectively, in the Western countries (Parkin et al, 2005). The value of screening for prostate cancer using serum prostate-specific antigen (PSA) remains controversial even after the publication of the two major randomised controlled trials of screening (Andriole et al, 2009; Schroder et al, 2009). Early detection of prostate cancer by screening can prevent death for a subset of men, but overdiagnosis and overtreatment may be substantial. The European Study of Screening for Prostate Cancer showed that to prevent one death from prostate cancer, 1410 men would need to be screened and 48 would need treatment (Schroder et al, 2009), although more mature data may demonstrate greater effectiveness. In all, 8 out of 1000 men undertaking PSA testing are likely to be overdiagnosed (Pashayan et al, 2009). In breast cancer, the benefit of mammographic screening in preventing death is greater than the harm in terms of overdiagnosis. On the basis of the UK Breast Screening Programme, 2.3 out of 1000 women screened for 20 years are likely to be overdiagnosed (Duffy et al, 2010).

Genome-wide association studies (GWAS) have identified genetic variants that are common in the population and confer susceptibility to different types of cancers. Most susceptibility variants identified by GWAS in different cancers have low effect size (per-allele relative risks of 1.1 – 1.3) (Chung et al, 2010) and so the clinical utility of the individual variants in predicting future risk is limited. However, the combination of multiple risk alleles, each with a weak effect may result in a distribution of risk in the population that is sufficiently wide to be clinically useful (Pharoah et al, 2002).

Several studies have shown that risk-profiles based on the known common susceptibility alleles have limited discrimination for breast cancer (Gail, 2008; Pharoah et al, 2008; Wacholder et al, 2010) and for prostate cancer (Salinas et al, 2009), leading some investigators to conclude that the clinical utility of risk prediction based on polygenic profiling is still limited. However, discrimination is not the only measure of clinical utility of a risk prediction model and it has been suggested that polygenic risk profiling may provide sufficient information to enable screening for breast cancer to be targeted to those women at highest risk (Pharoah...
et al, 2008; Devilee and Rookus, 2010; Wacholder et al, 2010). The aim of this study was to model the efficiency of a personalised screening strategy based on a combination of age and polygenic risk-profile compared with a strategy based on age alone in prostate and breast cancer.

MATERIALS AND METHODS

We compared the number of individuals eligible for screening and the number of cases potentially detectable by screening in the population undergoing screening based on age alone compared with a population undergoing personalised screening based on age and polygenic risk-profile, in which eligibility for screening depends on 10-year absolute risk of being diagnosed with prostate or breast cancer.

Absolute risk calculation

The number of prostate and breast cancer registrations, deaths from prostate and breast cancer, deaths from all causes, and mid-year population estimates in 1-year age bands for England from 2002 to 2006 were obtained from the Office for National Statistics. These data were used to estimate prostate and breast cancer incidence and mortality rates for prostate cancer, breast cancer, and other causes. We then used the DevCan 6.4.1 software (National Cancer Institute and Information Management Services, 2009) to derive the age-conditional absolute risk (risk between ages x and y, given alive and cancer-free at age x) of being diagnosed with prostate or breast cancer among the general population. DevCan is based on competing risk methods developed by Fay et al (2003). We also estimated age-conditional absolute risk for individuals at different levels of polygenic risk by underlying cancer-specific incidence with the polygenic relative risk.

Polygenic risk distribution

In all, 31 prostate cancer and 18 breast cancer susceptibility loci with common risk alleles have been published (Table 1).

We estimated the variance of the distribution of polygenic risk in the population from the published risk allele frequencies and per-allele relative risk, assuming a log-additive model of interaction between risk alleles both within and between loci. Under this model, the distribution of risk on a relative risk scale in the population from the published risk allele frequencies and other causes. We then used the DevCan 6.4.1 software (National Cancer Institute and Information Management Services, 2009) to derive the age-conditional absolute risk (risk between ages x and y, given alive and cancer-free at age x) of being diagnosed with prostate or breast cancer among the general population. DevCan is based on competing risk methods developed by Fay et al (2003). We also estimated age-conditional absolute risk for individuals at different levels of polygenic risk by underlying cancer-specific incidence with the polygenic relative risk.

RESULTS

Prostate cancer

On average, there were 22 836 new cases of prostate cancer per year in men 45–79 years in England during the period 2002 to 2006 (total population 8 655 126). The age-conditional absolute risk of being diagnosed with prostate over 10 years in the general population of men in England is shown in Figure 1. Under the age-based screening programme, 63% of men would be eligible for screening (aged 55 and over) and 96% of cases would occur in this subset of the population (Table 2). These are the cases that are potentially screen detectable. Under the personalised strategy, 53% of men would be eligible for screening with 93 of cases being screen detectable. Thus, the number of men eligible for screening would be 17% fewer at a cost of detecting 3% fewer cases. For the population of men aged 45–79 in England, there would be an additional three screen-detectable cases per 100 000 population in men younger than 55 years of age with polygenic risk ≥2%, and 12 cases per 100 000 population would be missed in men older than 55 years with polygenic risk <2%.

The proportion of men 45–79 years that would be eligible for screening and the proportion of cases potentially detectable within the eligible population at different risk thresholds are given in Figure 2.

The eligible population for the personalised approach based on a 1.4% 10-year risk threshold would be the same size as the age 55 and over population. The number of screen-detectable cases would then be 0.4% (one case per 100 000 population) greater under the personalised approach. Alternatively, a 1.5% threshold for personalised screening would be 2.6% (1637 men eligible for screening per 100 000 population) smaller than the age 55 and over population and have the same number of screen-detectable cases. At a higher age threshold, such as a 2.2% threshold for personalised screening, the number eligible for screening would be 4% (1983 per 100 000 population) smaller than the age 58 and over population and have the same number of potentially screen-detectable cases.

Table 2 shows the eligible population and screen-detectable cases for screening from age 51 or an absolute risk threshold of 1%, and screening from age 58 or an absolute risk threshold of 3%.

If all possible susceptibility variants for prostate cancer were known (predicted polygenic variance 1.58), 35% of men aged 45–79 would be at 2% 10-year risk with 90% of cases being potentially screen detectable. Compared with screening from age 55, 44% fewer men would be offered screening at a cost of 7% fewer cases being potentially screen detectable. To detect the same number of cases as screening from age 55, 20% (12 768 men eligible for screening per 100 000 population) fewer men would be eligible for screening (Figure 3).

Breast cancer

On average, there were 30 936 new cases of breast cancer per year in women 35–79 years in England during the period 2002–2006 (total population 13 126 890). The age-conditional absolute risk of being diagnosed with breast cancer over 10 years in the general population of women in England is given in Figure 1. Under the age-based programme, 65% of women aged 35–79 would be eligible for screening with 85% of cases being potentially screen
Table 1 Common susceptibility variants for prostate and breast cancer identified through GWAS

| dbSNP No. | Locus/gene | Risk-allele frequency | Odds ratio per allele | Variance | Reference |
|-----------|------------|-----------------------|-----------------------|----------|-----------|
| rs12621278 | 2q31/ITGA6 | 0.94                  | 1.30                  | 0.008    | Eeles et al (2009) |
| rs721048   | 2p15      | 0.19                  | 1.15                  | 0.002    | Gudmundsson et al (2008) |
| rs1465618  | 2p11/THADA | 0.23                  | 1.08                  | 0.002    | Eeles et al (2009) |
| rs2660753  | 3p12      | 0.11                  | 1.18                  | 0.002    | Eeles et al (2008) |
| rs10934853 | 3q21.3    | 0.28                  | 1.12                  | 0.002    | Gudmundsson et al (2009) |
| rs7679673  | 4q24/TET2  | 0.55                  | 1.09                  | 0.004    | Eeles et al (2009) |
| rs1701918  | 4q22/PTD1M5 | 0.66                | 1.10                  | 0.003    | Eeles et al (2009) |
| rs12500426 | 4q22/PTD1M6 | 0.46                | 1.08                  | 0.007    | Eeles et al (2009) |
| rs9364554  | 6q25      | 0.29                  | 1.17                  | 0.013    | Eeles et al (2008) |
| rs6465657  | 7q21      | 0.46                  | 1.12                  | 0.007    | Eeles et al (2008) |
| rs10486567 | 7p15/IAZFI | 0.77                  | 1.12                  | 0.009    | Thomas et al (2008) |
| rs2928679  | 8p21      | 0.42                  | 1.05                  | 0.010    | Eeles et al (2009) |
| rs1512268  | 9p13.1    | 0.45                  | 1.18                  | 0.014    | Eeles et al (2009) |
| rs628961   | 8q24      | 0.61                  | 1.28                  | 0.024    | Al Olama et al (2009) |
| rs10086908 | 8q24      | 0.70                  | 1.25                  | 0.007    | Al Olama et al (2009) |
| rs445114   | 8q24      | 0.64                  | 1.14                  | 0.041    | Gudmundsson et al (2009) |
| rs1690294  | 8q24      | 0.15                  | 1.21                  | 0.015    | Gudmundsson et al (2009) |
| rs6932367  | 8q24      | 0.50                  | 1.26                  | 0.010    | Yeager et al (2007) |
| rs1447295  | 8q24      | 0.10                  | 1.62                  | 0.004    | Arundadottir et al (2006) |
| rs16901799 | 9q24      | 0.03                  | 2.10                  | 0.002    | Gudmundsson et al (2007a) |
| rs4962416  | 10q26/CTBP2 | 0.27                | 1.17                  | 0.013    | Eeles et al (2008), Thomas et al (2008) |
| rs10993994 | 10q1/1/M5MB | 0.24                | 1.25                  | 0.014    | Eeles et al (2008), Thomas et al (2008) |
| rs7127900  | 11p15     | 0.20                  | 1.22                  | 0.011    | Eeles et al (2009) |
| rs7931342  | 11q13     | 0.51                  | 1.16                  | 0.012    | Eeles et al (2008), Thomas et al (2008) |
| rs4430796  | 17q12/HNF1B | 0.49               | 1.24                  | 0.015    | Gudmundsson et al (2007b) |
| rs1649974  | 17q12/HNF1B | 0.80               | 1.28                  | 0.015    | Gudmundsson et al (2007b) |
| rs1859962  | 17q24.3   | 0.46                  | 1.24                  | 0.017    | Gudmundsson et al (2007b) |
| rs2735839  | 19q32/2,3KLK2,3KLK3 | 0.85       | 1.20                  | 0.001    | Eeles et al (2008) |
| rs1802476  | 19q32.2   | 0.54                  | 1.12                  | 0.011    | Gudmundsson et al (2009) |
| rs5759167  | 22q13     | 0.53                  | 1.16                  | 0.015    | Eeles et al (2009) |
| rs5945619  | Xp11      | 0.28                  | 1.12                  | 0.002    | Eeles et al (2008), Gudmundsson et al (2008) |

| dbSNP No. | Locus/gene | Risk-allele frequency | Odds ratio per allele | Variance | Reference |
|-----------|------------|-----------------------|-----------------------|----------|-----------|
| rs11249433| 1p11.2     | 0.39                  | 1.16                  | 0.010    | Thomas et al (2009) |
| rs1045485 | 2q33/CASP9 | 0.85                  | 1.14                  | 0.004    | Cox et al (2007) |
| rs13387043| 2q35       | 0.49                  | 1.12                  | 0.006    | Milne et al (2009) |
| rs4973768 | 3p12/NEK10, SLC4A7 | 0.46       | 1.11                  | 0.005    | Ahmed et al (2009) |
| rs889312  | 5q11/MAP3K1 | 0.28               | 1.13                  | 0.006    | Easton et al (2007) |
| rs4415084 | 5p12/MRPS30 | 0.40               | 1.19                  | 0.015    | Stacey et al (2008) |
| rs2046210 | 6p12/ESR1  | 0.36                  | 1.29                  | 0.030    | Zheng et al (2009) |
| rs13281615| 8q24       | 0.40                  | 1.08                  | 0.003    | Easton et al (2007) |
| rs1011970 | 9p17.3     | 0.17                  | 1.09                  | 0.002    | Turnbull et al (2010) |
| rs2981582 | 10q26/FGFR2 | 0.38              | 1.26                  | 0.025    | Udler et al (2009) |
| rs2380205 | 10p15      | 0.43                  | 1.04                  | 0.002    | Turnbull et al (2010) |
| rs10995190| 10q21/ZNF365 | 0.85              | 1.16                  | 0.006    | Turnbull et al (2010) |
| rs704010  | 10q22      | 0.39                  | 1.07                  | 0.002    | Turnbull et al (2010) |
| rs614367  | 11q13      | 0.15                  | 1.15                  | 0.005    | Turnbull et al (2010) |
| rs3817198 | 11p15/LSP1  | 0.30                | 1.07                  | 0.002    | Easton et al (2007) |
| rs999737  | 14q24/RAD51L1 | 0.76            | 1.06                  | 0.001    | Thomas et al (2009) |
| rs1244362 | 16q21/TDOX3 | 0.25               | 1.20                  | 0.014    | Easton et al (2007), Stacey et al (2007) |
| rs6504950 | 17q/COX1Ix2 | 0.73               | 1.05                  | 0.001    | Ahmed et al (2009) |

Abbreviations: dbSNP = Single Nucleotide Polymorphism database; GWAS = genome-wide association study. Reported risk-allele frequency in Europeans.

Figure 1 Ten-year absolute risk of being diagnosed with prostate or breast cancer, England, 2002–2006.
Personalised screening would entail screening 2% fewer women (1477 women eligible for screening per 100,000 population) than the age 47 and over population and yield the same number of potentially screen-detectable cases.

In a best-case scenario analysis, assuming all possible susceptibility variants for breast cancer were known, 28% of women 35–79 years would be at 2.5% risk and 76% of the cases would occur in this group. Compared with screening from age 47, 57% fewer women would be offered screening at a cost of detecting 10% fewer cases. To detect the same number of cases as screening from age 47, 39% (25,678 women eligible for screening per 100,000 population) fewer women would need to be screened (Figure 3).

**DISCUSSION**

These data show that personalised screening with eligibility for screening based on an absolute risk that is dependent on age and polygenic risk and equivalent to the risk threshold for eligibility based on age alone could reduce the number of people eligible for screening while detecting the majority of the cancers identified through a programme based on age alone. Alternatively, screening the same number of individuals in a personalised screening programme could potentially detect a greater number of cases than a screening programme based on age alone.

However, we have estimated the proportion of the population to be offered screening and the proportion of cancer cases that might be screen detectable in this subgroup of the population, from the distribution of genetic risk in the population. The estimate of potentially detectable cases is based on cancer incidence derived from cancer registration and is independent of the detection rate by screening. Given the normal distribution of polygenic risk among the cases, and the number of cases in single age group, we estimated the proportion and the expected number of cases that will occur above a certain absolute risk threshold. We have not estimated the expected number of cases to be detected following a screening programme, as this would depend on screening.

**Table 2** Reclassification of population of 100,000 men 45–79 years eligible for screening and in whom prostate cancer could be detectable, under age-based or personalised screening strategies

| Personalised screening | Age-based screening |
|------------------------|---------------------|
| **Polygenic risk threshold** | **< 51 years** | **≥ 51 years** | **Total** |
| Population              | 20,355              | 9377               | 29,733        |
| < 1%                    | 2079               | 68,188             | 70,267       |
| Total                   | 22,434             | 77,566             | 100,000      |
| Cases                   | 2                  | 3                  | 5            |
| < 1%                    | 1                  | 258                | 259          |
| ≥ 1%                    | 3                  | 261                | 264          |

**Polygenic risk threshold** | **< 55 years** | **≥ 55 years** | **Total** |
| Population              | 33,802             | 13,328             | 47,130      |
| < 2%                    | 2841               | 30,029             | 52,871      |
| Total                   | 36,643             | 63,357             | 100,000     |
| Cases                   | 6                  | 12                 | 18          |
| < 2%                    | 3                  | 243                | 246         |
| ≥ 2%                    | 9                  | 255                | 264         |

**Polygenic risk threshold** | **< 58 years** | **≥ 58 years** | **Total** |
| Population              | 46,499             | 16,152             | 60,408      |
| < 3%                    | 49,933             | 35,960             | 39,592      |
| Total                   | 51,492             | 52,113             | 100,000     |
| Cases                   | 15                 | 26                 | 41          |
| < 3%                    | 7                  | 216                | 223         |
| ≥ 3%                    | 22                 | 242                | 264         |

Eligibility based on age or polygenic risk equivalent to 10-year absolute for that age considering three scenarios: age 51 vs risk 1%, age 55 vs risk 2%, age 58 vs risk 3%; England 2002–2006.

![Figure 2](image1.png)

**Figure 2** Men eligible for screening and cases detectable by screening at different risk thresholds. Percentage of men 45–79 years of age with polygenic risk for prostate cancer greater than a given threshold risk and percentage of men with detectable prostate cancer within this high-risk population, England, 2002–2006.

![Figure 3](image2.png)

**Figure 3** Change in proportion of individuals eligible for screening with increase in the known susceptibility variants. The likely percentage fewer individuals that would be eligible for screening under the personalised screening strategy as compared with the standard screening while detecting the same number of cases with increase in the percentage of the known susceptibility alleles. Prostate: compared with screening men 55–79; currently ~24% of the variants known. Breast: compared with screening women 47–79; currently ~9% of the variants known.

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programme sensitivity. Screening programme sensitivity is the probability of detecting cancer by screening in a population subjected to screening. The programme sensitivity increases with decrease in the inter-screening interval, with increase in test sensitivity and with increase in the duration of the pre-clinical screen-detectable phase (Launoy et al, 1998). In subjects of a given age at high genetic risk, the test sensitivity is likely to be the same or better than in those of the same age at low genetic risk. However, both the PSA test (Hoffman et al, 2002) and mammogram are less sensitive in younger subjects (at lower risk). It is not known how test sensitivity will compare between younger and older subjects at the same absolute risk. The duration of the pre-clinical, screen-detectable phase may also vary by underlying genetic risk. Thus, the comparative sensitivity of the screening programme under the two approaches is not known, and empirical data will be needed in order to estimate this. Assuming equivalent or improved screening programme sensitivity, personalised screening has the potential for cost saving as the cost of the genetic test for risk profiling may be offset by savings on repeat screening and diagnostic work-up of false positives.

Reducing the number of screening tests may also reduce some of the harms associated with screening. Fewer screening tests will, at the population level, reduce the anxiety and inconvenience associated with having the test. Assuming that the probability of a false positive is independent of polygenic risk-profile, reducing the number of screen tests will also reduce the number of false-positive screens, with a reduction in the harms associated with a false positive and the benefit of saving further resources on diagnostic tests. Personalised screening also has the potential to reduce the harms associated with overdiagnosis and overtreatment, but this depends on the nature of the relationship between polygenic risk and disease aggressiveness. To date, there is equivocal evidence on the association of combination of prostate cancer susceptibility variants with disease aggressiveness (Xu et al, 2008; Bao et al, 2010).

Personalised screening may potentially confer additional benefits. It can detect cancer in younger subjects at high risk. Prostate and breast cancer detected in younger subjects may tend to behave more aggressively (Fredholm et al, 2009; Lin et al, 2009). If polygenic high risk is associated with disease aggressiveness, then potentially additional life years would be gained by early detection of cancer in younger subjects. The majority of breast cancer susceptibility variants identified to date confer risk for oestrogen receptor-positive breast cancers (Turnbull et al, 2010), which are responsive to hormonal treatment and have a favourable prognosis (Dunnwald et al, 2007). However, the nature of the complex interaction between disease risk, tumour subtype, natural history of disease, and benefit from screening are not understood and the true benefits of screening according to genetic risk cannot be estimated.

In addition to polygenic risk, there is scope for individualised screening based on phenotypic risk markers. Already, there is considerable screening activity below the age range of the UK national programme for women with a significant family history of breast cancer (Maurice et al, 2006). There is also interest in tailoring screening to risk based on mammographic breast density. This might be used to prescribe screening frequency or indeed modality, since in addition to risk, density affects the sensitivity and the potential lead time of mammographic screening (Chiu et al, 2010). Further studies are needed using empirical data to test the implications of adding information on PSA test level and family history to polygenic risk profiling for personalised screening in prostate cancer (Zheng et al, 2008).

The threshold risk for individualised screening will be population specific. We have used data from England to estimate the proportion of men 45–79 years that would be eligible for screening and the proportion of cases potentially detectable within the eligible population at different risk thresholds. The optimum threshold risk for population of England will be different from that of another population with different incidence of cancer, such as of Asian population with low incidence of prostate cancer.

Other issues need to be considered. Screening based on a personalised risk-profile would add complexity to a screening programme. Perhaps of greater importance is the fact that eligibility for screening based on age is generally acceptable to both professionals and the public, but whether eligibility based on age and other risk factors would also be acceptable is not known. Furthermore, there are ethical and legal issues associated with genetic testing and risk prediction that would need to be addressed before personalised programmes could be implemented.

Personalised screening strategy based on age and genetic risk would potentially improve the efficiency of screening programmes and reduce their adverse consequences. Questions remain whether higher genetic risk affects cancer detection and cancer behaviour and so affecting test sensitivity, overdiagnosis and outcome. Further evidence from empirical data is needed. Nevertheless, this approach has the potential to inform public health policy decision making in the context of population screening.

**Table 3**

| Personalised screening | Age-based screening |
|------------------------|---------------------|
| **Polygenic risk threshold** | **<47 years** | **≥47 years** | **Total** |
| Population | | | | |
| <2.5% | 30 276 | 19 926 | 50 202 |
| ≥2.5% | 4429 | 45 368 | 49 798 |
| Total | 34 705 | 65 295 | 100 000 |
| Cases | | | | |
| <2.5% | 26 | 38 | 64 |
| ≥2.5% | 9 | 162 | 172 |
| Total | 35 | 200 | 236 |

Eligibility based on age 47 or polygenic risk equivalent to 10-year absolute risk for age 47 (2.5% 10-year absolute risk); England 2002–2006.

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**Authors’ contributions**

PP developed the concept. NP and PP contributed to designing the methodology, analysis, interpretation of the findings, and drafting the paper. SWD contributed to designing the analysis. SC collated the data and contributed to the analysis. SWD, SC, TD, HB, DNF, DFE, and RE contributed to the interpretation of the results and revising of the paper. All authors have read and approved the final paper. NP and PP had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Conflict of interest**

The authors declare no conflict of interest.
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