**Supplementary table 1:** Total number of cases and controls in PRACTICAL III and GWAS stage 3 by population and study

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Ethnicity | No. | Study Acronym | Study Design | Controlsb | Casesb | Totalb | Agec |
| PRACTICAL  PIII | European | 1 | Aarhus | Case-Control | 592 | 650 | 1,242 | 64 (36-88) |
| 2 | BiPAS | Case-Control | 88 | 176 | 264 | 69 (51-85) |
| 3, 4 | CPCS 1 & 2 | Case-Control | 1,474 | 413 | 1,887 | 69 (50-94) |
| 5 | ESTHER | Case-Control | 329 | 330 | 659 | 66 (51-75) |
| 6 | FHCRC | Case-Control | 1,265 | 1,309 | 2,574 | 60 (35-74) |
| 7 | HaPCS | Case-Control | 485 | 499 | 984 | 66 (41-81) |
| 8 | MAYO a | Case-Control | 527 | 884 | 1,411 | 65 (41-86) |
| 9 | MCCS | Case-Controld | 2,332 | 491 | 2,823 | 69 (50-85) |
| 10 | MEC | Cohort Studye | 396 | 448 | 844 | 59 (46-71) |
| 11 | MOFFITT | Case-Control | 372 | 702 | 1,074 | 69 (50-87) |
| 12 | PCFSa | Case-Controlf | 82 | 76 | 158 | 65 (42-87) |
| 13 | PCMUS | Case-Control | 193 | 173 | 366 | 70 (47-90) |
| 14 | Poland | Case-Control | 572 | 574 | 1,146 | 68 (43-90) |
| 15 | ProtecT | Case-Controlg | 2,194 | 2,204 | 4,398 | 63 (45-72) |
| 16 | QLD | 3 studies h | 1,394 | 1,346 | 2,740 | 63 (40-89) |
| 17 | SFPCS (NC-CCPC) | Case-Control | 219 | 302 | 521 | 65 (44-80) |
| 18 | TAMPERE | Case-Control | 1,851 | 2,496 | 4,347 | 67 (37-95) |
| 19 | TASPRACa | Case-Control | 337 | 492 | 829 | 62 (44-82) |
| 20 | UKGPCS | Case-Control | 212 | 392 | 604 | 60 (36-85) |
| 21 | ULM a | Case-Control | 379 | 702 | 1,081 | 64 (42-84) |
| 22 | USC | Case-Control | 295 | 488 | 783 | 68 (46-94) |
| 23 | UTAH a | Case-Control | 240 | 466 | 706 | 67 (42-87) |
| 24 | Valais | Case-Control | 222 | 170 | 392 | 65 (49-84) |
| **Total** | | | | | **16,050** | **15,783** | **31,833** | **64 (35-95)** |
|  | | | | | | | | |
| GWAS stage 3 | European |  | MCCS | Case-Controld | 548 | 327 | 875 | 69 (49-85) |
|  | PCFSb | Case-Controlf | 218 | 1,025 | 1,243 | 57 (41-87) |
| 25 | SEARCH | Case-Control | 1,365 | 1,450 | 2,815 | 63 (44-73) |
|  | UKGPCS | Case-Control | 1,945 | 1,703 | 3,648 | 61 (36-85) |
| **Total** | | | | | **4,076** | **4,505** | **8,581** | **61 (36-87)** |
|  | | | | | | | | |
| **Total European (PRACTICAL & GWAS stage 3)** | | | | | **20,126** | **20,288** | **40,414** | **64 (35-95)** |
| **Total European (PRACTICAL & GWAS stage 3) excluding familial studies** | | | | | **18,343** | **16,643** | **34,986** | **64 (35-95)** |

a Studies that oversampled cases with family history. b The number of samples given here are those that were available for this analysis. These may differ from the numbers for the complete studies given in the Supplementary Notes. c Mean age at diagnosis for cases (min-max). d Nested case-control. e Population-based prospective cohort study. f Population-based with cases from informative families. g PSA screening selected cases-controls. h One Cohort study, one hospital based and one prospective cohort study.

**Supplementary Table 2**: Data information for family history and age at diagnosis/observation

|  |  |  |  |
| --- | --- | --- | --- |
| **(a): All samples excluding studies with familial design** | | | |
| Samples | Cases | Controls | Total |
| Without family history | 9,740 | 8,305 | 18,045 |
| With family history | 2,165 | 999 | 3,164 |
| Total having information | 11,905 | 9,304 | **21,209** |
| Missing family history information | 4,738 | 9,039 | 13,777 |
| Total | 16,643 | 18,343 | 34,986 |
| Family history information | 71.53% | 50.72% | **60.62%** |
| Percentage of samples with family history among those having family history information | **18.19%** | **10.74%** | **14.92%** |
| Age at diagnosis/recruitment | 16,503 | 14,647 | **31,150** |
| Mean age (range) | **64 (35-95)** | **58.3 (18-99)** | 61.5 (18-99) |
| Missing age information | 140 | 3,696 | 3,836 |
| Total | 16,643 | 18,343 | 34,986 |
| Percentage of samples with age information | 99.16% | 79.85% | 89.04% |
| **(b): All samples** | | | |
| Samples | Cases | Controls | Total |
| Without family history | 11,940 | 9,451 | 21391 |
| With family history | 3,486 | 1,397 | 4,883 |
| Total having information | 15,426 | 10,848 | **26,274** |
| Missing family history information | 4,862 | 9,278 | 14,140 |
| Total | 20,288 | 20,126 | 40,414 |
| Family history information | 76.04% | 53.90% | **65.01%** |
| Percentage of samples with family history among those having family history information | **22.60%** | **12.88%** | 18.58% |
| Age at diagnosis/recruitment | 20,137 | 16,262 | **36,399** |
| Mean age (range) | 64 (35-95) | 58.7 (18-99) | 61.6 (18-99) |
| Missing age information | 151 | 3,864 | 4,015 |
| Total | 20,288 | 20,126 | 40,414 |
| Percentage of samples with age information | 99.26% | 80.80% | **90.07%** |

**Supplementary Table 3:** Grade-specific and family history-specific odds ratios.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Variable/  Marker | GS **<** 8 | GS 8 + | *P*a | *P*b | Family History (FH) | | *P*c |
| No | Yes |
| PRSd | 1.75 (1.68-1.82) | 1.65 (1.54-1.77) | .37 | NA | 1.70 (1.64-1.76) | 1.79 (1.63-1.96) | 1.8x10-4 |
| rs721048 | 1.13 (1.08-1.18) | 1.12 (1.02-1.23) | .81 | .96 | 1.09 (1.06-1.16) | 1.11 (1.04-1.19) | .06 |
| rs1465618 | 1.08 (.1.04-1.13) | 1.00 (.92-1.09) | .09 | .22 | 1.07 (1.03-1.12) | 1.13 (1.05-1.21) | .02 |
| rs12621278 | .76 (.70-.82) | .75 (.64-.88) | .79 | 1.00 | .72 (.66-.78) | .77 (.67-.88) | .21 |
| rs2660753 | 1.12 (1.05-1.19) | 1.05 (.94-1.18) | .29 | .82 | 1.15 (1.08-1.22) | 1.07 (.98-1.18) | .87 |
| rs17021918 | .88 (.85-.91) | .94 (.88-1.01) | .03 | .007 | .87 (.84-.90) | .92 (.86-.98) | .21 |
| rs12500426 | 1.11 (1.07-1.15) | 1.02 (.95-1.10) | .05 | .29 | 1.10 (1.06-1.14) | 1.10 (1.03-1.18) | .43 |
| rs7679673 | .86 (.83-.89) | .90 (.84-.97) | .16 | .15 | .90 (.87-.93) | .84 (.79-.89) | 2.9x10-5 |
| rs9364554 | 1.11 (1.07-1.16) | 1.03 (.95-1.12) | .16 | .60 | 1.08 (1.03-1.12) | 1.18 (1.11-1.26) | .15 |
| rs10486567 | .83 (.79-.88) | .81 (.73-.90) | .79 | .90 | .87 (.83-.92) | .80 (.73-.88) | .01 |
| rs6465657 | 1.09 (1.05-1.13) | 1.06 (.99-1.14) | .64 | .21 | 1.08 (1.04-1.12) | 1.14 (1.07-1.21) | .07 |
| rs1447295 | 1.41 (1.34-1.49) | 1.48 (1.33-1.64) | .64 | .001 | 1.41 (1.33-1.49) | 1.54 (1.42-1.68) | 1.4x10-6 |
| rs6983267 | .82 (.79-.85) | .84 (.79-.91) | .68 | .85 | .83(.80-.86) | .79 (.75-.84) | .003 |
| rs16901979 | 1.48 (1.35-1.62) | 1.77 (1.50-2.08) | .06 | .13 | 1.58 (1.44-1.73) | 1.63 (1.42-1.87) | .05 |
| rs2928679 | 1.05 (1.01-1.09) | 1.00 (.93-1.08) | .51 | .33 | 1.05 (1.01-1.09) | 1.08 (1.02-1.15) | .06 |
| rs1512268 | 1.16 (1.12-1.20) | 1.04 (.97-1.12) | .002 | .02 | 1.13 (1.09-1.17) | 1.19 (1.12-1.26) | .16 |
| rs4962416 | 1.06 (1.02-1.11) | 1.02 (.94-1.11) | .35 | .80 | 1.04 (.99-1.08) | 1.07 (1.00-1.14) | .13 |
| rs10993994 | 1.23 (1.19-1.28) | 1.21 (1.13-1.30) | .82 | .80 | 1.24 (1.20-1.29) | 1.32 (1.25-1.41) | .002 |
| rs7931342 | .85 (.82-.88) | .79 (.74-.86) | .19 | .50 | .85 (.82-.89) | .80 (.75-.85) | 9.6x10-5 |
| rs7127900 | 1.28 (1.22-1.34) | 1.14 (1.04-1.24) | .01 | .003 | 1.21 (1.16-1.27) | 1.27 (1.18-1.37) | .01 |
| rs4430796 | .80 (.77-.83) | .79 (.74-.85) | .98 | .40 | .82 (.79-.85) | .77 (.73-.82) | .004 |
| rs11649743 | .87 (.83-.91) | .87 (.79-.95) | .94 | .30 | .89 (.85-.94) | .83 (.77-.90) | .003 |
| rs1859962 | 1.19 (1.15-1.24) | 1.13 (1.05-1.21) | .20 | .78 | 1.17 (1.13-1.21) | 1.21 (1.14-1.28) | .007 |
| rs2735839 | .79 (.75-.83) | .93 (.83-1.03) | .002 | .003 | .81 (.76-.85) | .80 (.73-.88) | .31 |
| rs5759167 | .85 (.82-.88) | .85 (.80-.91) | .85 | .58 | .85 (.82-.88) | .82 (.77-.86) | .04 |
| rs5945619 | 1.13 (1.10-1.17) | 1.16 (1.09-1.23) | .54 | .44 | 1.14 (1.10-1.18) | 1.10 (1.04-1.16) | .81 |

a *P*-value for difference in per-allele OR between GS 8+ and GS <8

b *P*-value for trend in OR by Gleason score as an ordinal variable

c *P*-value for difference in per-allele OR between Family History Yes and No

d Polygenic Risk Score adjusted for age at diagnosis and family history. For Family history, PRS adjusted for age at diagnosis (OR is based on per unit increase of PRS).

**Supplementary Table 4:** PSA levels by genotype in controls.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Marker | Geometric mean PSA (95%CI) | | | *P*-valuea |
| rs721048 | CC | CT | TT |  |
| 2.07 (1.63-2.50) | 1.78 (1.39-2.16) | 2.04 (.70-3.38) | .11 |
| rs1465618 | GG | GA | AA |  |
| 1.42 (1.37-1.47) | 1.40 (1.32-1.47) | 1.30 (1.16-1.45) | .29 |
| rs12621278 | AA | AG | GG |  |
| 1.94 (1.61-2.26) | 2.03 (1.08-2.97) | 1.68 (1.14-2.23) | .81 |
| rs2660753 | GG | GA | AA |  |
| 1.90 (1.58-2.22) | 2.06 (1.37-2.75) | 7.01 (-4.66-18.67) | .21 |
| rs17021918 | GG | GA | AA |  |
| 1.94 (1.48-2.39) | 1.87 (1.42-2.31) | 2.26 (1.21-3.30) | .34 |
| rs12500426 | GG | GT | TT |  |
| 2.07 (1.43-2.71) | 2.24 (1.65-2.83) | 1.98 (1.07-2.88) | .19 |
| rs7679673 | CC | CA | AA |  |
| 1.75 (1.34-2.16) | 2.25 (1.69-2.81) | 1.48 (1.34-1.63) | .38 |
| rs9364554 | CC | CT | TT |  |
| 2.40 (1.79-3.00) | 1.63 (1.36-1.90) | 1.38 (1.27-1.49) | .25 |
| rs10486567 | GG | GA | AA |  |
| 2.80 (1.90-3.70) | 2.26 (1.36-3.16) | 1.44 (1.17-1.71) | .12 |
| rs6465657 | AA | AG | GG |  |
| 1.78 (1.35-2.22) | 2.05 (1.57-2.53) | 2.07 (1.38-2.76) | .83 |
| rs1447295 | GG | GT | TT |  |
| 2.08 (1.70-2.46) | 1.54 (1.25-1.84) | 1.11 (.93-1.29) | .03 |
| rs6983267 | CC | CA | AA |  |
| 2.04 (1.32-2.76) | 2.12 (1.65-2.59) | 1.61 (1.22-1.99) | .01 |
| rs16901979 | GG | GT | TT |  |
| 1.94 (1.62-2.26) | 1.56 (1.38-1.75) | 1.30 (.69-1.91) | .18 |
| rs2928679 | CC | CT | TT |  |
| 1.61 (1.31-1.92) | 2.17 (1.63-2.70) | 1.91 (1.26-2.57) | .27 |
| rs1512268 | GG | GA | AA |  |
| 1.68 (1.30-2.06) | 2.13 (1.59-2.66) | 1.99 (1.33-2.64) | .004 |
| rs4962416 | AA | AG | GG |  |
| 2.06 (1.59-2.53) | 1.97 (1.50-2.45) | 1.35 (1.21-1.49) | .73 |
| rs10993994 | GG | GA | AA |  |
| 2.15 (1.54-2.77) | 1.68 (1.38-1.98) | 2.45 (1.50-3.40) | 3.5x10-5 |
| rs7931342 | CC | CA | AA |  |
| 2.36 (1.62-3.09) | 2.06 (1.57-2.56) | 1.41 (1.33-1.49) | .11 |
| rs7127900 | GG | GA | AA |  |
| 1.90 (1.54-2.25) | 1.99 (1.35-2.64) | 2.90 (.33-5.47) | .03 |
| rs4430796 | AA | AG | GG |  |
| 1.54 (1.34-1.74) | 2.08 (1.61-2.54) | 2.22 (1.41-3.03) | .38 |
| rs11649743 | GG | GA | AA |  |
| 2.13 (1.69-2.57) | 1.57 (1.27-1.86) | 2.59 (.44-4.75) | .84 |
| rs1859962 | TT | TG | GG |  |
| 2.05 (1.49-2.60) | 1.99 (1.50-2.48) | 1.84 (1.34-2.33) | .17 |
| rs2735839 | GG | GA | AA |  |
| 2.07 (1.70-2.43) | 1.79 (1.15-2.42) | 1.08 (.83-1.32) | 2.8x10-13 |
| rs5759167 | GG | GT | TT |  |
| 1.86 (1.28-2.43) | 2.16 (1.63-2.69) | 1.59 (1.26-1.93) | .37 |
| rs5945619 | TT | TC | CC |  |
| 2.63 (1.80-3.46) |  | 2.24 (1.53-2.94) | .09 |

aTest for trend in log (PSA) by allele dose

**Supplementary Table 5:** Age-specific odds ratios.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Variable/  Marker | Age at diagnosis (years) | | | | | *P*trenda |
| <55 | 55-59 | 60-64 | 65-69 | 70+ |
| PRSb | 1.76  (1.62-1.92) | 1.85  (1.72-1.98) | 1.70  (1.59-1.82) | 1.70  (1.57-1.83) | 1.48  (1.37-1.60) | 2.6x10-4 |
| rs721048 | 1.09  (.99-1.19) | 1.13  (1.06-1.21) | 1.12  (1.05-1.19) | 1.13  (1.06-1.20) | 1.07  (.99-1.15) | .86 |
| rs1465618 | 1.14  (1.04-1.24) | 1.07  (1.01-1.13) | 1.09  (1.03-1.15) | 1.09  (1.03-1.16) | 1.01  (.94-1.07) | .03 |
| rs12621278 | .59  (.49-.71) | .76  (.67-.86) | .67  (.60-.76) | .79  (.71-.88) | .83  (.73-.94) | 1.9x10-5 |
| rs2660753 | 1.16  (1.04-1.29) | 1.10  (1.01-1.20) | 1.18  (1.09-1.28) | 1.13  (1.05-1.22) | 1.04  (.95-1.14) | .12 |
| rs17021918 | .83  (.77-.90) | .86  (.81-.91) | .91  (.87-.96) | .89  (.85-.94) | .89  (.84-.94) | .06 |
| rs12500426 | 1.17  (1.08-1.27) | 1.16  (1.09-1.24) | 1.09  (1.03-1.15) | 1.05  (1.00-1.11) | 1.07  (1.02-1.13) | .08 |
| rs7679673 | .87  (.81-.94) | .87  (.82-.92) | .90  (.85-.94) | .86  (.81-.90) | .89  (.85-.94) | .08 |
| rs9364554 | 1.15  (1.06-1.24) | 1.13  (1.07-1.20) | 1.08  (1.02-1.14) | 1.08  (1.03-1.14) | 1.07  (1.01-1.14) | .07 |
| rs10486567 | .78  (.69-.87) | .82  (.76-.89) | .90  (.84-.97) | .87  (.81-.93) | .85  (.78-.92) | .19 |
| rs6465657 | 1.14  (1.07-1.23) | 1.11  (1.05-1.17) | 1.11  (1.05-1.16) | 1.06  (1.01-1.11) | 1.09  (1.03-1.15) | .69 |
| rs1447295 | 1.42  (1.28-1.57) | 1.43  (1.33-1.55) | 1.39  (1.29-1.49) | 1.40  (1.30-1.51) | 1.45  (1.33-1.58) | .75 |
| rs6983267 | .80  (.74-.85) | .80  (.75-.84) | .80  (.76-.84) | .82  (.78-.87) | .90  (.85-.95) | .06 |
| rs16901979 | 1.54  (1.31-1.81) | 1.53  (1.35-1.73) | 1.53  (1.36-1.73) | 1.56  (1.39-1.75) | 1.60  (1.39-1.84) | .06 |
| rs2928679 | 1.08  (1.01-1.17) | 1.03  (.97-1.09) | 1.02  (.96-1.07) | 1.04  (.99-1.10) | 1.04  (.98-1.11) | .09 |
| rs1512268 | 1.11  (1.04-1.20) | 1.19  (1.13-1.26) | 1.15  (1.09-1.21) | 1.13  (1.08-1.19) | 1.10  (1.05-1.16) | .70 |
| rs4962416 | 1.12  (1.03-1.21) | 1.01  (.95-1.07) | 1.08  (1.02-1.14) | 1.01  (.96-1.07) | 1.01  (.95-1.09) | .37 |
| rs10993994 | 1.35  (1.26-1.45) | 1.28  (1.22-1.36) | 1.21  (1.15-1.28) | 1.23  (1.17-1.29) | 1.16  (1.10-1.23) | .009 |
| rs7931342 | .83  (.77-.89) | .84  (.79-.88) | .82  (.77-.86) | .87  (.82-.91) | .86  (.81-.92) | .22 |
| rs7127900 | 1.39  (1.27-1.51) | 1.24  (1.16-1.32) | 1.22  (1.15-1.30) | 1.24  (1.17-1.32) | 1.15  (1.08-1.23) | .01 |
| rs4430796 | .80  (.75-.86) | .77  (.73-.82) | .81  (.77-.85) | .85  (.81-.89) | .83  (.79-.89) | .12 |
| rs11649743 | .91  (.83-.99) | .87  (.81-.93) | .85  (.79-.90) | .91  (.85-.97) | .90  (.83-.97) | .33 |
| rs1859962 | 1.25  (1.17-1.34) | 1.20  (1.14-1.27) | 1.24  (1.18-1.30) | 1.13  (1.07-1.18) | 1.11  (1.05-1.18) | .04 |
| rs2735839 | .77  (.70-.86) | .72  (.67-.79) | .77  (.72-.83) | .85  (.79-.91) | .91  (.84-.99) | .001 |
| rs5759167 | .80  (.75-.86) | .84  (.79-.88) | .84  (.80-.88) | .84  (.80-.88) | .87  (.82-.91) | .11 |
| rs5945619 | 1.14  (1.07-1.21) | 1.19  (1.14-1.25) | 1.16  (1.12-1.21) | 1.11  (1.07-1.15) | 1.07  (1.02-1.12) | .0003 |

a 1df trend test for trend in OR by age, using case only analysis.

b OR is based on per unit increase of PRS.

**Supplementary Table 6:** The results of 29 pair wise interaction of 25 SNPs

significant at P <0.05 (29 out of 300 interactions; Bonferroni correction 0.05/300=1.67x10-4).

|  |  |  |  |
| --- | --- | --- | --- |
| Pair | *P*-valuea | Pair | *P*-valuea |
| rs721048 x rs17021918 | 0.05 | rs9364554 x rs1859962 | 0.003 |
| rs1465618 x rs17021918 | 0.004 | rs10486567 x rs16901979 | 0.01 |
| rs1465618 x rs12500426 | 0.001 | rs10486567 x rs4962416 | 0.02 |
| rs1465618 x rs7679673 | 0.03 | rs10486567 x rs4430796 | 0.004 |
| rs1465618 x rs7127900 | 0.02 | rs1447295 x rs7127900 | 0.04 |
| rs2660753 x rs12500426 | 0.02 | rs16901979 x rs10993994 | 0.001 |
| rs2660753 x rs16901979 | 0.04 | rs4962416 x rs7931342 | 0.03 |
| rs2660753 x rs2928679 | 0.05 | rs4962416 x rs4430796 | 0.01 |
| rs2660753 x rs5759167 | 0.04 | rs4962416 x rs2735839 | 0.001 |
| rs17021918 x rs7679673 | 0.01 | rs10993994 x rs4430796 | 0.02 |
| rs12500426 x rs7679673 | 0.02 | rs7931342 x rs4430796 | 0.02 |
| rs12500426 x rs11649743 | 0.04 | rs7931342 x rs2735839 | 0.05 |
| rs12500426 x rs5759167 | 0.04 | rs7127900 x rs4430796 | 0.02 |
| rs7679673 x rs5759167 | 0.01 | rs4430796 x rs2735839 | 0.004 |
| rs9364554 x rs16901979 | 0.001 |  |  |

a Likelihood ratio test

**Supplementary Table 7:** Estimated odds ratios of PRS percentiles adjusted for age at diagnosis of PrCa (five categories) in a model allowing for an interaction between PRS and Age.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Covariate | | Odds ratio (95% CI) | *P*-value | Odds ratioa (95% CI) | *P*-value |
| PRS Group | <1% | 1 |  | 0.10 (0.05-0.18) | 2.4x10-13 |
| 1-10% | 3.43 (1.89-6.23) | 5.3x10-5 | 0.33 (0.27-0.41) | 3.7x10-26 |
| 10-25% | 5.90 (3.22-10.82) | 9.5x10-9 | 0.57 (0.50-0.65) | 2.5x10-18 |
| 25-75% | 10.33 (5.53-19.29) | 2.5x10-13 | 1 |  |
| 75-90% | 19.12 (9.92-36.86) | 1.3x10-18 | 1.85 (1.66-2.07) | 6.6x10-28 |
| 90-99% | 28.92 (14.50-57.69) | 1.3x10-21 | 2.80 (2.38-3.30) | 1.5x10-34 |
| >=99% | 58.11 (26.99-125.11) | 3.1x10-25 | 5.63 (4.05-7.82) | 6.4x10-25 |
| Family History (Yes/No) | | 2.52 (2.29-2.78) | 4.7x10-77 | 2.52 (2.29-2.78) | 4.7x10-77 |
| PRS x Age at Diagnosis  interactionb | | 0.97 (0.95-0.99) | 0.003 | 0.97 (0.95-0.99) | 0.003 |

a Odds Ratios were compared to median risk group.

b PRS and age at diagnosis both as categorical variables.

**Supplementary Table 8:** Estimated odds ratios used for estimating absolute risk

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **(a)** Model without interaction | | | | | | | |
| Family History (FH) | Risk Group | | | | | | |
| <1% | 1-10% | 10-25% | 25-75% | 75-90% | 90-99% | >=99% |
| No | 0.14 | 0.41 | 0.63 | 1.00 | 1.68 | 2.31 | 4.24 |
| Yes | 0.35 | 1.04 | 1.60 | 2.52 | 4.24 | 5.83 | 10.70 |
| **(b)** Model with interactiona (samples with no FH) | | | | | | | |
| Age group | <1% | 1-10% | 10-25% | 25-75% | 75-90% | 90-99% | >=99% |
| <55 | 0.10 | 0.33 | 0.57 | 1.00 | 1.85 | 2.80 | 5.63 |
| 55-59 | 0.09 | 0.31 | 0.55 | 1.00 | 1.79 | 2.62 | 5.09 |
| 60-64 | 0.08 | 0.29 | 0.53 | 1.00 | 1.73 | 2.45 | 4.60 |
| 64-69 | 0.07 | 0.27 | 0.52 | 1.00 | 1.67 | 2.29 | 4.16 |
| 70+ | 0.06 | 0.25 | 0.50 | 1.00 | 1.62 | 2.14 | 3.76 |
| **(c)** Model with interactiona (samples with FH) | | | | | | | |
| Age group | <1% | 1-10% | 10-25% | 25-75% | 75-90% | 90-99% | >=99% |
| <55 | 0.24 | 0.84 | 1.44 | 2.52 | 4.67 | 7.07 | 14.21 |
| 55-59 | 0.22 | 0.78 | 1.39 | 2.52 | 4.52 | 6.61 | 12.84 |
| 60-64 | 0.20 | 0.73 | 1.35 | 2.52 | 4.37 | 6.18 | 11.60 |
| 64-69 | 0.18 | 0.68 | 1.30 | 2.52 | 4.22 | 5.78 | 10.49 |
| 70+ | 0.16 | 0.64 | 1.26 | 2.52 | 4.08 | 5.40 | 9.48 |

a Interaction between PRS and age at diagnosis both as categorical variables.