



# Genome-wide association study of prostate cancer-specific survival

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## Genome-wide association study of prostate cancer-specific survival

*A full list of authors and affiliations appears at the end of the article.*

### Abstract

**Background**—Unnecessary intervention and overtreatment of indolent disease are common challenges in clinical management of prostate cancer. Improved tools to distinguish lethal from indolent disease are critical.

**Methods**—We performed a genome-wide survival analysis of cause-specific death in 24,023 prostate cancer patients (3,513 disease-specific deaths) from the PRACTICAL and BPC3 consortia. Top findings were assessed for replication in a Norwegian cohort (CONOR).

**Results**—We observed no significant association between genetic variants and prostate cancer survival.

**Conclusions**—Common genetic variants with large impact on prostate cancer survival were not observed in this study.

**Impact**—Future studies should be designed for identification of rare variants with large effect sizes or common variants with small effect sizes.

### Introduction

Prostate cancer is the second leading cause of cancer death among men in the developed world. Randomized trials have shown that PSA-based screening can reduce prostate cancer mortality up to 40%, though at the cost of considerable over-diagnosis and over-treatment of indolent disease(1). Thus, improved tools to distinguish lethal from indolent disease to guide clinicians in treatment decisions are critical. Epidemiological studies support the existence of a genetic component to prostate cancer prognosis(2). The purpose of this study was to identify Single Nucleotide Polymorphisms (SNPs) associated with prostate cancer specific survival. We performed a genome-wide search among individuals from two large prostate cancer genetics consortia (PRACTICAL(3) and BPC3(4) with replication of top findings in a Norwegian prostate cancer cohort (CONOR)(5).

\*Corresponding author: Robert Szulkin, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, SE-171 77 Stockholm, Sweden. Tel: +46 8 524 822 21. Fax: +46 8 31 49 75. robert.szulkin@ki.se.

\*\*Full list of participants of The PRACTICAL Consortium is provided in the Supplementary Notes

**Conflict of Interest:** There is no conflict of interest.

## Materials and Methods

### Study populations and genotyping

In total, 24,023 prostate cancer patients with follow-up on cause specific death from the PRACTICAL (n = 21,241) and BPC3 (n = 2,782) consortia were included in the present study (Table 1). All men from BPC3 have an aggressive disease, defined by a tumor Gleason score of eight or above. Participants had either been genotyped on a custom designed SNP chip (iCOGS) with 211,155 markers or on standard genome-wide arrays (Table 1). Imputation was performed using a cosmopolitan panel from the 1000 Genomes Project (March 2012) to increase the genetic coverage. Only SNPs that had an imputation quality above 0.75 and minor allele frequency (MAF) above 1% were assessed (1.2–9.5 million SNPs in each separate study, Table 1). Detailed information regarding study populations, genotyping and imputation is found in (3) and (4).

### Statistical analysis

Within each study, SNPs were assessed for association with disease survival, assuming an additive genetic effect, in a Cox regression model allowing for left truncation and right censoring of observational times. Results were combined in fixed-effects meta-analysis. In the discovery stage, we considered an association to be genome-wide significant if the overall meta-analysis achieved  $p < 5E-08$  and the test for heterogeneity across studies was non-significant ( $p > 0.05$ ). We also adjusted the most associated SNPs for population structure (principal components), age at diagnosis, diagnostic PSA and Gleason score but we did not observe any confounding (data not shown).

### Replication

Genome-wide significant SNPs in the discovery stage were directly genotyped in 1,783 individuals from the UKGPCS1 study (Table 1) using TaqMan assays to verify imputation quality, evaluated as the concordance rate between imputed and genotyped data (percentage of individuals correctly classified by imputation). Significant SNPs from the discovery stage with satisfactory imputation qualities were assessed for replication in a Norwegian case-cohort study (CONOR(5)) comprising 1,496 prostate cancer cases of which 791 died due to prostate cancer during follow-up. Genotypes were derived through TaqMan assays and analyzed in a proportional hazards model for case-cohort designs(6) with adjustment for age at diagnosis.

## Results

Among the 24,023 prostate cancer patients included in the discovery stage, we observed 3,513 deaths due to prostate cancer (Table 1). No inflation was observed in the combined meta-analysis ( $\lambda_{1000} = 1.02$ )(7). Ten SNPs reached genome-wide significance, two common variants (MAF 7–8%) and eight rare variants (MAF 1–2%, Table 2). Six of these SNPs failed genotyping in the UKGPCS1 sample (either because of unsuccessful assay design, failed clustering or monomorphism) while the remaining four SNPs (rs114997855 on chromosome 2, rs76010824 on chromosome 3, rs140659849 and rs723557 on chromosome X) had an excellent concordance rate (98–99%) between genotyped and imputed data. These

four SNPs were put forward for replication in the Norwegian CONOR cohort. None of the four SNPs showed any evidence of association in the Norwegian cohort ( $p > 0.05$ ) and inclusion of these results in the meta-analysis resulted in non-genome-wide significance levels for each SNP (Table 2).

## Discussion

We performed a genome-wide search for SNPs associated with prostate cancer survival by combining data from the PRACTICAL and BPC3 consortia. Our null finding is in line with previous smaller studies(8) and implicates that the existence of common genetic variants with large effect sizes is unlikely. We would however like to stress that our analysis was based on imputed data and some areas of the genome were not well represented due to a low number of SNPs with good imputation quality.

Despite a reasonably large replication sample we saw no evidence of association among the four SNPs that were initially found to be genome-wide significant ( $p < 5E-08$ ). Two of these SNPs were rare, in which spurious associations occur more easily. It is however more surprising that the two common SNPs (MAF=7–8%) were false positives. This underlines the importance of independent replication in genetic association studies.

From this study, we conclude that the search for SNPs that are associated with prostate cancer survival should focus on the identification of rare variants with large effect sizes or common variants with small effect sizes. Large study populations with complete follow-up information regarding survival are warranted to successfully achieve this task.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Authors

Robert Szulkin<sup>1,2,\*</sup>, Robert Karlsson<sup>1</sup>, Thomas Whittington<sup>1</sup>, Markus Aly<sup>1</sup>, Henrik Gronberg<sup>1</sup>, Rosalind A. Eeles<sup>3,4</sup>, Douglas F. Easton<sup>5</sup>, Zsafia Kote-Jarai<sup>3</sup>, Ali Amin Al Olama<sup>5</sup>, Sara Benlloch<sup>5</sup>, Kenneth Muir<sup>6,7</sup>, Graham G. Giles<sup>8,9</sup>, Melissa C. Southey<sup>10</sup>, Liesel M. FitzGerald<sup>8</sup>, Brian E. Henderson<sup>11</sup>, Fredrick R. Schumacher<sup>11</sup>, Christopher A. Haiman<sup>11</sup>, Csilla Sipeky<sup>12</sup>, Teuvo LJ Tammela<sup>14</sup>, Børge G. Nordestgaard<sup>15,16</sup>, Timothy J. Key<sup>17</sup>, Ruth C. Travis<sup>17</sup>, David E. Neal<sup>18,19</sup>, Jenny L. Donovan<sup>20</sup>, Freddie C. Hamdy<sup>21</sup>, Paul D.P. Pharoah<sup>22</sup>, Nora Pashayan<sup>23,22</sup>, Kay-Tee Khaw<sup>24</sup>, Janet L. Stanford<sup>25,26</sup>, Stephen N. Thibodeau<sup>27</sup>, Shannon K. McDonnell<sup>27</sup>, Daniel J. Schaid<sup>27</sup>, Christiane Maier<sup>28</sup>, Walther Vogel<sup>29</sup>, Manuel Luedeke<sup>28</sup>, Kathleen Herkommer<sup>30</sup>, Adam S. Kibel<sup>31</sup>, Cezary Cybulski<sup>32</sup>, Jan Lubinski<sup>32</sup>, Wojciech Klu niak<sup>32</sup>, Lisa Cannon-Albright<sup>33,34</sup>, Hermann Brenner<sup>35,36,37</sup>, Volker Herrmann<sup>35</sup>, Bernd Holleczek<sup>38</sup>, Jong Y. Park<sup>39</sup>, Thomas A. Sellers<sup>39</sup>, Hui-Yi Lim<sup>40</sup>, Chavdar Slavov<sup>41</sup>, Radka P. Kaneva<sup>42</sup>, Vanio I. Mitev<sup>42</sup>, Amanda Spurdle<sup>43</sup>, Manuel R. Teixeira<sup>44,45</sup>, Paula Paulo<sup>44</sup>, Sofia Maia<sup>44</sup>, Hardev Pandha<sup>46</sup>, Agnieszka Michael<sup>46</sup>, Andrzej Kierzek<sup>46,\*\*</sup> **on behalf of the PRACTICAL consortium**, Jyotsna Batra<sup>47</sup>, Judith A. Clements<sup>47,47,48</sup> **on behalf of The**

**Australian Prostate Cancer BioResource**, Demetrius Albanes<sup>49</sup>, Gerald L. Andriole<sup>50</sup>, Sonja I. Berndt<sup>49</sup>, Stephen Chanock<sup>49,51</sup>, Susan M. Gapstur<sup>52</sup>, Edward L. Giovannucci<sup>53,54</sup>, David J. Hunter<sup>55</sup>, Peter Kraft<sup>55</sup>, Loic Le Marchand<sup>56</sup>, Jing Ma<sup>54,57,58</sup>, Alison M. Mondul<sup>49</sup>, Kathryn L. Penney<sup>54,57,58</sup>, Meir J. Stampfer<sup>58</sup>, Victoria L. Stevens<sup>52</sup>, Stephanie J. Weinstein<sup>49</sup>, Antonia Trichopoulou<sup>59,60,61</sup>, Bas H. Bueno-de-Mesquita<sup>62,63,64,65</sup>, Anne Tjonneland<sup>66</sup>, David G. Cox<sup>67,68</sup> **on behalf of the BPC3 consortium**, Lovise Maehle<sup>69</sup>, Johanna Schleutker<sup>12,13</sup>, Sara Lindström<sup>55</sup>, and Fredrik Wiklund<sup>1</sup>

## Affiliations

<sup>1</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden <sup>2</sup>Academic Primary Healthcare Center, Stockholm county council, Karolinska Institute, Stockholm, Sweden <sup>3</sup>The Institute of Cancer Research, London, UK <sup>4</sup>Royal Marsden National Health Service (NHS) Foundation Trust, London and Sutton, UK <sup>5</sup>Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge CB1 8RN, UK <sup>6</sup>Institute of Population Health, University of Manchester, Manchester, UK <sup>7</sup>Warwick Medical School, University of Warwick, Coventry, UK <sup>8</sup>Cancer Epidemiology Centre, Cancer Council Victoria, 615 St Kilda Road, Melbourne Victoria, Australia <sup>9</sup>Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Victoria, Australia <sup>10</sup>Genetic Epidemiology Laboratory, Department of Pathology, The University of Melbourne, Grattan Street, Parkville, Victoria 3010, Australia <sup>11</sup>Department of Preventive Medicine, Keck School of Medicine, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, California, US <sup>12</sup>Department of Medical Biochemistry and Genetics, Institute of Biomedicine Kiinamyllynkatu 10, FI-20014 University of Turku, Finland <sup>13</sup>BioMediTech, University of Tampere and FimLab Laboratories, Tampere, Finland. <sup>14</sup>Department of Urology, Tampere University Hospital and Medical School, University of Tampere, Finland <sup>15</sup>Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark <sup>16</sup>Faculty of Health and Medical Sciences, University of Copenhagen <sup>17</sup>Cancer Epidemiology, Nuffield Department of Population Health University of Oxford, Oxford, UK <sup>18</sup>University of Cambridge, Department of Oncology, Box 279, Addenbrooke's Hospital, Hills Road Cambridge CB2 0QQ <sup>19</sup>Cancer Research UK Cambridge Research Institute, Li Ka Shing Centre, Cambridge, UK <sup>20</sup>School of Social and Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS, UK <sup>21</sup>Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK, Faculty of Medical Science, University of Oxford, John Radcliffe Hospital, Oxford, UK <sup>22</sup>Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge, UK <sup>23</sup>University College London, Department of Applied Health Research, 1-19 Torrington Place, London, WC1E 7HB <sup>24</sup>Clinical Gerontology Unit, University of Cambridge, Cambridge UK <sup>25</sup>Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle,

Washington, 98109-1024, USA <sup>26</sup>Department of Epidemiology, School of Public Health, University of Washington, Seattle, Washington, US <sup>27</sup>Mayo Clinic, Rochester, Minnesota, USA <sup>28</sup>Department of Urology, University Hospital Ulm, Germany <sup>29</sup>Institute of Human Genetics, University Hospital Ulm <sup>30</sup>Department of Urology, Klinikum rechts der Isar der Technischen Universitaet Muenchen, Munich, Germany <sup>31</sup>Division of Urologic Surgery, Brigham and Womens Hospital, Dana-Farber Cancer Institute, 75 Francis Street, Boston, MA 02115, USA <sup>32</sup>International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland <sup>33</sup>Division of Genetic Epidemiology, Department of Medicine, University of Utah School of Medicine, Salt Lake City, Utah, USA <sup>34</sup>George E. Wahlen Department of Veterans Affairs Medical Center, Salt Lake City, Utah, US <sup>35</sup>Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany <sup>36</sup>Division of Preventive Oncology, German Cancer Research Center (DKFZ), Heidelberg Germany <sup>37</sup>German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany <sup>38</sup>Saarland Cancer Registry, Saarbrücken, Germany <sup>39</sup>Department of Cancer Epidemiology, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA <sup>40</sup>Biostatistics Program, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA <sup>41</sup>Department of Urology and Alexandrovska University Hospital, Medical University, Sofia, Bulgaria <sup>42</sup>Department of Medical Chemistry and Biochemistry, Molecular Medicine Center, Medical University, Sofia, 2 Zdrave Str., 1431 Sofia, Bulgaria <sup>43</sup>Molecular Cancer Epidemiology Laboratory, Queensland Institute of Medical Research, Brisbane, Australia <sup>44</sup>Department of Genetics, Portuguese Oncology Institute, Porto, Portugal <sup>45</sup>Biomedical Sciences Institute (ICBAS), University of Porto, Porto, Portugal <sup>46</sup>The University of Surrey, Guildford, Surrey, GU2 7XH <sup>47</sup>Australian Prostate Cancer Research Centre-Qld, Institute of Health and Biomedical Innovation and School of Biomedical Science, Queensland University of Technology, Brisbane, Australia <sup>48</sup>Australian Prostate Cancer BioResource, Brisbane, QLD <sup>49</sup>Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA <sup>50</sup>Washington University School of Medicine, St. Louis, MO, USA <sup>51</sup>Core Genotyping Facility, Frederick National Laboratory for Cancer Research, Gaithersburg MD, USA <sup>52</sup>Epidemiology Research Program, American Cancer Society, 250 Williams Street, Atlanta Georgia 30303, USA <sup>53</sup>Departments of Epidemiology and Nutrition, Harvard T.H. Chan School of Public Health, Boston MA, 02115, USA <sup>54</sup>Department of Medicine, Harvard Medical School, Boston MA, 02115, USA <sup>55</sup>Program in Genetic Epidemiology and Statistical Genetics, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA <sup>56</sup>Cancer Research Center of Hawaii, University of Hawaii, Honolulu, HI 96813, USA <sup>57</sup>Department of Epidemiology, Brigham and Women's Hospital Channing Laboratory, Boston MA 02115, USA <sup>58</sup>Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115 <sup>59</sup>Hellenic Health Foundation, 13 Kaisareias Street, Athens, GR-115 27, Greece <sup>60</sup>Department of Hygiene, Epidemiology and Medical Statistics, University of Athens Medical School, 75 M. Asias Street, Goudi, GR-115 27,

Athens, Greece <sup>61</sup>Bureau of Epidemiologic Research, Academy of Athens, 23 Alexandroupoleos Street, Athens, GR-115 27, Greece <sup>62</sup>Dt. for Determinants of Chronic Diseases (DCD), National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands <sup>63</sup>Dt. of Gastroenterology and Hepatology, University Medical Centre, Utrecht, The Netherlands <sup>64</sup>Dt. of Epidemiology and Biostatistics, The School of Public Health, Imperial College London, London, United Kingdom <sup>65</sup>Dt. of Social & Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia <sup>66</sup>Danish Cancer Society Research Center, Copenhagen, Denmark <sup>67</sup>Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London <sup>68</sup>Cancer Research Center of Lyon, INSERM UMR1052, Center Léon Bérard, Lyon, France <sup>69</sup>Inherited Cancer Research Group, Department for Medical Genetics, The Norwegian Radium Hospital, Oslo University Hospital, 0310, Oslo, Norway

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Table 1

Patient characteristics of included study populations.

Study	N	No of prostate cancer deaths	Total person-years	Person-years at risk median (min-max)	Number of SNPs with imputation quality $\geq 0.75$
<b>PRACTICAL</b>					
CAPS	412	49	3 476.6	9.3 (0.4–11.8)	5,752,274 <sup>f</sup>
CAPSI	492	214	3 120.2	7.1 (0.1–11.8)	8,933,855 <sup>\$</sup>
CAPS2	1493	331	11 644.6	9.1 (0–11.8)	8,715,366 <sup>\$</sup>
CPCS	925	97	1 772.1	1.3 (0.1–18.1)	5,550,954 <sup>f</sup>
EPIC	404	35	467.4	0 (0–13.2)	5,503,395 <sup>f</sup>
ESTHER	300	22	2 179.9	7.7 (0.1–9.8)	5,495,692 <sup>f</sup>
FHCRC	760	46	7 716.6	8.1 (0.2–18.1)	5,532,283 <sup>f</sup>
MAYO	737	40	4 612.8	6.8 (0.1–13.9)	5,555,791 <sup>f</sup>
MCCS_PCF5	1663	139	41 656.4	22.6 (0–71.2)	5,425,082 <sup>f</sup>
MEC	581	15	3 531.5	5.8 (0.1–13.1)	5,462,203 <sup>f</sup>
PCMUS	57	7	68.9	1.1 (0.1–4.0)	5,359,978 <sup>f</sup>
SEARCH	1369	70	4 966.3	3.7 (0.1–4.5)	5,510,831 <sup>f</sup>
STHMI	2199	71	8 247.2	3.9 (0–4.3)	5,724,947 <sup>f</sup>
TAMPERE	2463	248	21 037.6	7.8 (0.8–20.9)	6,455,082 <sup>f</sup>
UKGPCS	4344	826	22 906.2	4.3 (0–27.3)	5,485,041 <sup>f</sup>
UKGPCS1	1783	457	13 689.0	7.0 (0.1–30.0)	9,536,409 <sup>V</sup>
UKGPCS2	772	189	6 961.8	9.1 (0–24.9)	1,235,003 <sup>T</sup>
ULM	365	32	3 151.9	9.0 (0.6–22.0)	5,457,321 <sup>f</sup>
UTAH	122	27	603.7	4.0 (0.1–26.9)	5,641,408 <sup>f</sup>
<b>BPC3</b>					
ATBC	245	133	1 426.2	5.8 (0–19.9)	8,232,459 <sup>\$</sup>



Study	N	No of prostate cancer deaths	Total person-years	Person-years at risk median (min-max)	Number of SNPs with imputation quality $\geq 0.75$
<b>PRACTICAL</b>					
CPSII	636	79	5 859,4	9.2 (0.3–16.3)	7,448,367 <sup>§</sup>
EPIC	431	159	2 197,3	5.2 (0–14.3)	7,612,553 <sup>§</sup>
HPFS	214	37	1 616.6	7.6 (0.1–14.4)	7,539,277 <sup>§</sup>
MEC	244	23	1 868,3	7.7 (0.9–15.4)	7,571,269 <sup>§</sup>
PHS	298	97	2 811,8	9.4 (0–24.7)	7,569,352 <sup>§</sup>
PLCO	714	70	4 664,5	6.7 (0.1–12.9)	7,526,690 <sup>§</sup>
<b>Total</b>	<b>24023</b>	<b>3513</b>	<b>182 254,8</b>		
<hr/>					
CONOR	1496	791	8741,4	5.0 (0.08–20.8)	

<sup>f</sup> Genotyped on a custom Illumina SNP infirmum chip (iCOGS) with 211,155 SNPs, enriched in regions associated with incidence of prostate, breast and ovarian cancer.

<sup>g</sup> Genotyped on Illumina Infinium HumanHap 550 Array.

<sup>h</sup> Genotyped on Illumina iSELECT in 43,671 SNPs.

<sup>i</sup> Genotyped on Affymetrix GeneChip 5.0K or 500K.

<sup>j</sup> Genotyped on Illumina Human 610 or 610K.

**Table 2**

Genome-wide assessment of prostate cancer survival.

SNP CHR:BP	Alleles <sup>T</sup> MAF	PRACTICAL and BPC3		CONOR		All studies <sup>S</sup>	
		Total number No of PC/deaths	HR (95% CI) P-value	HR (95% CI) P-value	HR (95% CI) P-value		
rs190087062	G/A	2,416/704	2.83 (1.99–4.02)				
1:115063785	0.02		6.5E-09				
rs114997855	A/G	20,051/2,729	1.75 (1.44–2.13)	0.88 (0.42–1.85)	1.67 (1.38–2.03)		
2:30622824	0.02		2.6E-08	0.73	1.20E-07		
rs76010824	A/G	23,251/3,324	1.29 (1.18–1.41)	1.01 (0.76–1.35)	1.26 (1.16–1.38)		
3:67442642	0.07		2.8E-08	0.94	1.10E-07		
rs184342703	T/C	6,812/832	2.36 (1.73–3.20)				
4:135989066	0.02		4.2E-08				
rs192864713	G/A	1,738/464	3.54 (2.31–5.43)				
5:27429220	0.01		7.3E-09				
rs111414857	G/A	17,146/2,236	1.98 (1.56–2.50)				
7:126639415	0.01		1.7E-08				
rs149470135	A/T	4,725/599	3.09 (2.09–4.59)				
8:86472701	0.01		2.0E-08				
rs117643112	C/A	6,306/1,577	1.93 (1.53–2.43)				
12:81746712	0.02		3.1E-08				
rs140659849 <sup>P</sup>	A/G	2,702/271	3.00 (2.06–4.36)	0.75 (0.24–2.33)	2.61 (1.83–3.73)		
X:50194937	0.01		9.6E-09	0.62	1.20E-07		
rs723557Y	G/T	23,251/3,324	1.17 (1.10–1.24)	1.00 (0.84–1.19)	1.15 (1.09–1.22)		
X:126653357	0.08		1.5E-07	0.98	6.10E-07		

Abbreviations: CHR=Chromosome, BP=Base position (Genome build 37), MAF=Minor allele frequency, HR=Hazard ratio, 95% CI=95% confidence interval.

<sup>T</sup>Minor allele/Major allele. Minor allele used as effect allele (major as reference) in analysis.

<sup>S</sup>Meta-analysis between PRACTICAL, BPC3 and CONOR.

<sup>P</sup>Proxy for rs13440791 (p=2.7E-08 in PRACTICAL and BPC3).

Proxy for rs190977150 (p=9.5E-09 in PRACTICAL and BPC3).

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