#### **Supplementary Figures**



Supplementary Figure 1. Quantile-quantile plots for the stage 1 meta-analysis.

QQ plot after filtering out SNPs with MAF < 0.01. Red line includes all SNPs; green line excludes SNPs +/- 500kb of previously identified locus.







# Supplementary Figure 3. Regional association LD plots













			Heterogene	ity P-value		
RSID	Position	BMI	Hypertension	Sex	Smoking	Notes
rs4381241	chr1:50907438	0.1260	0.2971	0.9800	0.4365	
rs13376700	chr1:51477643	0.1441	0.8296	0.5867	0.7499	
rs6706003	chr2:46563392	0.7553	0.5484	0.4456	0.9480	
rs6755594	chr2:46589295	0.0072	0.5257	0.3656	0.4870	
rs72851889	chr2:144694129	0.4763	0.0759	0.9594	0.7222	
rs72855540	chr2:144990548	0.6065	0.1736	0.3559	0.7988	
rs67311347	chr3:40533243	0.9734	0.9460	0.2067	0.4066	
rs2203002	chr3:141796239	0.6793	0.3010	0.5532	0.8355	
rs10936602	chr3:169536637	0.0577	0.6883	0.0866	0.2242	
rs234043	chr3:172313367	0.4390	0.3124	0.9282	0.2813	
rs7697932	chr4:101005318	0.7494	0.0033	0.4040	0.0074	
rs17050872	chr4:131097748	0.5047	0.8624	0.4159	0.5546	
rs76912165	chr5:92965344	0.0322	0.8506	0.1022	0.5913	
rs1266819	chr6:52094946	0.8495	0.4585	0.0836	0.8467	
rs59294613	chr7:124554267	0.8329	0.3840	0.9974	0.0082	
rs73149977	chr7:134488864	0.8895	0.4190	0.6981	0.0130	
rs2889	chr8:22875909	0.2791	0.5079	0.2006	0.4373	
rs2241261	chr8:22876739	0.1427	0.4912	0.5391	0.6539	
rs7913447	chr10:73992040	0.7282	0.8890	0.8155	0.1781	
rs11813268	chr10:105682296	0.8877	0.6983	0.1433	0.2921	
rs77774900	chr11:95830733	0.5445	0.0733	0.8029	0.1773	
rs1800057	chr11:108143456	0.2800	0.6833	0.0614	0.8114	
rs74911261	chr11:108357137	0.2001	0.6537	0.1407	0.5375	
rs77736197	chr12:107623706	0.9695	0.4229	0.5077	0.0973	
rs72730336	chr14:73248661	0.2424	0.7131	0.0043	0.9807	Stronger effect in females; some heterogeneity observed among males
rs8007348	chr14:73272730	0.2646	0.7935	0.0026	0.9964	Stronger effect in females
rs4903064	chr14:73279420	0.2630	0.8311	<0.0001	0.1338	Stronger effect in females; some heterogeneity observed among females
rs2109794	chr14:73288855	0.2743	0.6162	<0.0001	0.2676	Stronger effect in females
rs11637556	chr15:66728951	0.2492	0.8158	0.9727	0.7230	
rs4804368	chr19:7190290	0.6837	0.1725	0.5010	0.0194	

# Supplementary Figure 4. SNP analyses stratified by sex, body mass index (BMI; <25, 25-29, 30+ kg/m2), smoking status (never, former, current), and history of diagnosed hypertension

Body Mass Index BMI 15-24 NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Heteroperity P-value= 0.1712		1.11 [ 0.92 . 1.34 0.96 [ 0.77 . 1.16 1.06 [ 0.77 . 1.40 1.26 [ 1.13 . 1.40] 1.21 [ 1.01 . 1.45 1.17 [ 1.08 . 1.26 ]
BMI 25-20 NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Atterogeneity P-value= 0.455		1.20 [1.03 1.39] 1.19 1.00 1.41 0.98 0.75 1.29 1.17 1.06 1.28 1.04 [0.90] 1.20 1.14 [1.07 1.21]
BMI 30-50 NCI 2 MDA JARC GWAS JARC Replication Combined Heterogeneity P-value= 0.6513		$\begin{array}{c} 1.01 & [0.83] & 1.22 \\ 1.16 & [0.44] & 1.43 \\ 0.88 & [0.66] & 1.20 \\ 1.07 & [0.87] & 1.21 \\ 1.05 & [0.97] & 1.13 \\ 1.05 & [0.97] &$
Heterogeneity P-value= 0.126	•	1.12[1.08,1.17]
Hypertension No History NC1 1 NC12 MDA JARC GWAS JARC Replication Combined Combined Heterogeneity P-value= 0.1727		1.18 [1.03 1.34] 1.07 [0.96 1.20] 0.92 [0.74 1.14] 1.05 [0.93 1.18] 0.83 [0.78 1.11] 1.06 [0.99 1.12]
History NCI 2 MDA IARC GWAS IARC Replication combined Heterogeneity P-value= 0.3635		1.07 [ 0.91 1.25] 1.05 [ 0.92 : 1.21] 1.22 [ 0.89 1.41] 1.22 [ 1.05 1.37] 1.00 [ 0.83 1.21] 1.11 [ 1.04 1.19]
Overall Heterogeneity P-value= 0.2971	•	1.08 [ 1.03 , 1.13 ]
Sex Male NCI 1 NCI 2 MDA MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.3894		1.16 [ 1.03 . 1.31 1.12 [ 1.05 . 1.23 1.05 [ 0.87 . 1.26 1.15 [ 1.07 . 1.23 1.02 [ 0.91 . 1.14 1.12 [ 1.07 . 1.17 ]
Female NCI 1 NCI 2 MDA JARC GWAS JARC Replication Combined Heterogeneity P-value= 0.0242		1.08 [0.90, 1.28] 0.96 [0.85, 1.08] 0.99 [0.74, 1.32] 1.17 [1.07, 1.27] 1.28 [1.11], 1.47] 1.12 [1.05, 1.18]
Overall Heterogeneity P-value= 0.98	◆	1.12 [ 1.08 , 1.16 ]
Smoking Net T Net 1 NC1 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.0763		$\begin{array}{c} 1.09 & [ 0.90 & .1.31 ] \\ 1.05 & [ 0.91 & .1.25 ] \\ 0.90 & [ 0.71 & .1.13 ] \\ 1.22 & [ 1.12 & .1.34 ] \\ 1.27 & [ 1.07 & .1.38 ] \\ 1.15 & [ 1.08 & .1.22 ] \end{array}$
Former NCI 1 MCI 2 MDA JARC GWAS JARC Replication Combined Heterogeneity P-value= 0.2781		1.04 [0.88, 1.22] 1.02 [0.88, 1.21] 1.11 [0.88, 1.43] 1.22 [0.88, 1.43] 1.20 [0.83, 1.21] 1.00 [0.83, 1.21] 1.10 [1.02, 1.19]
Current NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Atterogeneity P-value= 0.0975		1.29 [1.07 1.56] 1.20 [0.92 1.61] 1.29 [0.87 1.93] 1.05 [0.93 1.18] 0.93 [0.78 1.11] 1.08 [1.00 , 1.18]
Overall Heterogeneity P-value= 0.4365	◆	1.12 [ 1.08 , 1.17 ]
	0.50 1.00 1.50 2.00	
	Odds Ratio	





















Odds Ratio



Body Mass Index BMI 15-24 NCI 1		0.8810.56 1.381
NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.4978		0.98 0.85 1.56 1.76 0.84 3.67 0.90 0.71 1.13 0.84 0.57 1.23 0.93 0.76 1.09
BMI 25-29 NCI 1 NCI 2 MDA JARC Replication Combined Heterogeneity P-value= 0.988		$\begin{array}{c} 1.22 \left[ 0.83 \\ .13 \right] \left[ 0.78 \\ .164 \right] \\ 1.10 \left[ 0.56 \\ .2.16 \right] \\ 1.17 \left[ 0.96 \\ .143 \right] \\ 1.08 \left[ 0.82 \\ .143 \right] \\ 1.15 \left[ 1.00 \\ .1.32 \right] \end{array}$
BMI 30-50 NCI 1 MCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.1392		$\begin{array}{c} 1.47 & [ 0.91 & 2.39 ] \\ 0.98 & [ 0.61 & 1.57 ] \\ 0.87 & [ 0.46 & 1.65 ] \\ 1.13 & [ 0.87 & 1.47 ] \\ 1.76 & [ 1.24 & 2.51 ] \\ 1.25 & [ 1.06 & 1.49 ] \end{array}$
Combined Heterogeneity P-value= 0.0322	•	1.10[1.01,1.21]
Hypertension No History NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.6603		$\begin{array}{c} 1.10 & [ 0.86 & 1.64 ] \\ 1.01 & 0.78 & 1.31 \\ 1.35 & 0.80 & 2.31 \\ 0.94 & 0.73 & 1.21 \\ 1.10 & 0.78 & 1.64 \\ 1.05 & [ 0.92 & 1.21 ] \end{array}$
History NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.9085		$\begin{array}{c} 1.07 \left[ \begin{array}{c} 0.74 \\ .1.08 \end{array} \right] \left[ \begin{array}{c} 0.74 \\ .1.43 \end{array} \right] \\ 1.18 \left[ \begin{array}{c} 0.72 \\ .1.43 \end{array} \right] \\ 1.18 \left[ \begin{array}{c} 0.72 \\ .1.71 \end{array} \right] \\ 1.00 \left[ \begin{array}{c} 0.77 \\ .1.24 \end{array} \right] \\ 1.00 \left[ \begin{array}{c} 0.77 \\ .1.24 \end{array} \right] \\ 1.08 \left[ \begin{array}{c} 0.83 \\ .1.25 \end{array} \right] \end{array} \right]$
Overall Heterogeneity P-value= 0.8506	•	1.06[0.96,1.18]
Sex <u>Male</u> NCI 1 NCI 2 MDA JARC GWAS JARC Replication Combined Heterogeneity P-value= 0.7491		$\begin{array}{c} 1.18 \left[ \begin{array}{c} 0.88 \\ 1.03 \\ 0.84 \\ 1.26 \\ 1.07 \\ 0.71 \\ 1.07 \\ 0.27 \\ 1.26 \\ 1.07 \\ 0.92 \\ 1.07 \\ 1.16 \\ 1.04 \\ 0.94 \\ 1.15 \\ 1.04 \\ 0.94 \\ 1.15 \\ 1.04 \\ 0.94 \\ 1.15 \\ 1.04 \\ 0.94 \\ 1.15 \\ 1.04 \\ 0.94 \\ 1.15 \\ 1.04 \\ 0.94 \\ 1.15 \\ 1.04 \\ 0.94 \\ 1.15 \\ 1.04 \\ 0.94 \\ 1.15 \\ 1.04 \\ 0.94 \\ 1.15 \\ 1.04 \\ 0.94 \\ 1.15 \\ 1.04 \\ 0.94 \\ 1.15 \\ 1.04 \\ 0.94 \\ 1.15 \\ 1.04 \\ 0.94 \\ 1.15 \\ 1.04 \\ 0.94 \\ 1.15 \\ 1.04 \\ 0.94 \\ 1.15 \\ 1.04 \\ 0.94 \\ 1.15 \\ 1.05 \\ 1.04 \\ 1.0$
Female NCI 1 NCI 2 MDA JARC GWAS JARC Replication Combined Heterogeneity P-value= 0.0816		1.07 [0.69, 1.65] 1.19 [0.90, 1.67] 2.62 [1.17, 5.83] 1.04 [0.86, 1.26] 1.47 [1.13, 1.91] 1.19 [1.05, 1.35]
Averall Heterogeneity P-value= 0.1022		1.09[1.01,1.18]
Smoking Net F NCT 1 NCT 2 MDA MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.8908		$\begin{array}{c} 0.92 \left[ \begin{array}{c} 0.58 \\ .1.47 \\ 1.13 \\ 0.79 \\ .1.60 \\ 1.07 \\ 0.63 \\ .1.83 \\ 1.20 \\ 0.99 \\ .1.44 \\ 1.12 \\ 0.87 \\ .1.44 \\ 1.14 \\ 1.00 \\ .1.29 \\ \end{array} \right]$
Former NCI 1 NCI 2 MDA JARC Replication Combined Heterogeneity P-value= 0.3494		1.16 [0.79.1.72] 1.10 [0.76.1.61] 2.02 [1.08.37] 1.00 [0.77.1.29] 1.25 [0.84.1.84] 1.14 [0.97.1.34]
Current NCI 1 NCI 2 MDA JARC Replication IARC Replication Combined Heterogeneity P-value= 0.5422		1.38 [0.88, 2.17] 0.94 [0.47, 1.88] 0.73 [0.34, 1.60] 0.94 [0.73, 1.21] 1.10 [0.79, 1.54] 1.02 [0.86, 1.22]
Overall Heterogeneity P-value= 0.5913	· · · · · · · · · · · · · · · · · · ·	1.11 [ 1.02 , 1.21 ]
	0.00 1.00 2.00 3.00 4.00 5.00 6.00	

Odds Ratio

Body Mass Index BMI 15-24		
NCI 1 NCI 2		1.12 [ 0.93 , 1.34 ] 0.99 [ 0.82 , 1.20 ]
MDA IARC GWAS		1.27 0.91 1.77 1.00 0.90 1.12
ARC Replication Combined Heterogeneity P-value= 0.4731	•	1.05 [ 0.98 ; 1.13 ]
BMI 25-29		
NCI 1 NCI 2		0.98 [ 0.84 . 1.14 ] 1.04 [ 0.87 . 1.23 ]
MDA IARC GWAS		1.24 [ 0.93 , 1.65 ] 1.11 [ 1.01 , 1.22 ]
Combined Reterrogeneity P-value= 0.3267		1.06 0.99 1.12
BMI 30-50		
NCI 1 NCI 2		1.06 0.88 1.28 1.12 0.91 1.37
MDA IARC GWAS		0.97 0.71 1.32 1.01 0.89 1.14
IARC Replication Combined		0.99 0.85 1.17 1.03 0.95 1.11
Reterogeneity P=value= 0.8823		105(101 100)
Heterogeneity P-value= 0.8495		1.05[1.01,1.08]
Hypertension No History		
NCI 1 NCI 2		0.96[0.84.1.09] 1.06[0.95.1.19]
MDA IARC GWAS		1.24 [ 1.00 , 1.53 ] 0.98 [ 0.87 ; 1.10 ]
Combined		1.04 [ 0.95 , 1.32 ]
History		
NCI 1 NCI 2		1.15 0.98 1.35
MDA IARC GWAS		1.26 0.99 1.60
IARC Replication Combined		1.09 0.91 1.30 1.07 1.00 1.15
Heterogeneity P-value= 0.4302		
Heterogeneity P-value= 0.4585	•	1.05[1.01,1.10]
Sex Male		
NCI 1 NCI 2		1.01 [ 0.89 . 1.13 ] 1.05 [ 0.96 . 1.15 ]
MDA IARC GWAS	`┊┝╧╾╼ ┝┳┥	1.29 [ 1.07 ] 1.56 ] 1.01 [ 0.94 ] 1.08 ]
IARC Replication Combined		1.00 [ 0.90 . 1.12 ] 1.03 [ 0.99 ; 1.08 ]
Female		
NCI 1		1.13 [ 0.95 , 1.35 ]
MDA IARC GWAS		1.10 0.82 1.46
IARC Replication Combined		1.06 0.92 1.22
Heterogeneity P-value= 0.7434		
Overall Heterogeneity P-value= 0.0836	•	1.06 [ 1.02 , 1.09 ]
Smoking		
NCI 1 NCI 2		1.14 [ 0.95 , 1.37 ]
MDA IARC GWAS		0.97 0.76 1.23 1.12 1.02 1.22
IARC Replication Combined		0.95 0.83 1.08 1.05 0.99 1.12
Heterogeneity P-value= 0.1775		
NCI 1	⊢_ <mark>∎</mark>	0.96 [ 0.81 . 1.14 ]
MDA IARC GWAS		
ARC Replication		1.09 0.91 1.30
Heterogeneity P-value= 0.0632		
Current NCI 1		0.99 [ 0.83 . 1.18 ]
MDA IARC GWAS		
IARC Replication		
Heterogeneity P-value= 0.2701		1.00[0.00]1.11]
Overall Heterogeneity P-value= 0.8467	◆	1.05 [ 1.01 , 1.09 ]
	0.50 1.00 1.50 2.00 2.50	
	Odds Ratio	



Body Mass Index		
NCI 1 NCI 2		0.93 [ 0.76 , 1.14 ] 0.82 [ 0.66 , 1.02 ]
MDA IARC GWAS		0.91 0.63 1.32 0.94 0.84 1.06
IARC Replication Combined Heterogeneity P-value= 0.2619	•	1.14 [ 0.94 , 1.37 ] 0.95 [ 0.88 , 1.03 ]
BMI 25-29		
NCI 1 NCI 2		1.03 [ 0.88 , 1.22 ] 0.84 [ 0.70 , 1.01 ] 0.82 [ 0.80 , 1.25 ]
IARC GWAS IARC Replication		
Combined Heterogeneity P-value= 0.1016	◆ 1	0.93 [ 0.87 ] 0.99 ]
BMI 30-50 NCI 1		071[057_087]
NCI 2 MDA		0.01 0.74 1.13 1 1.14 0.82 1.59
IARC GWAS IARC Replication		0.96 [0.84 . 1.10] 1.04 [0.88 . 1.25]
Heterogeneity P-value= 0.0409	<b>—</b>	0.84[0.80, 1.02]
Combined Heterogeneity P-value= 0.8895	•	0.94 [ 0.90 , 0.98 ]
Hypertension No History		
NCI 1 NCI 2		
MDA IARC GWAS IARC Replication		
Combined Heterogeneity P-value= 0.3101	★	0.95 [ 0.89 ] 1.02 ]
History		0.00 [ 0.78 1.06 ]
NČI 2 MDA		0.85 0.74 0.99 1
IARC GWAS IARC Replication		0.00[0.79]1.02] 1.00[0.82]1.21]
Combined Heterogeneity P-value= 0.4993	◆	0.92 [ 0.85 , 0.98 ]
Qverall Aeterogeneity P-value= 0.419	◆	0.94 [ 0.89 , 0.98 ]
Sex Male		
NCI 1 NCI 2		0.95 [ 0.83 . 1.08 ] 0.90 [ 0.81 . 0.99 ]
MDA IARC GWAS	⊢	0.98 0.81 1.20 0.94 0.88 1.02
Combined Heterogeneity P-value= 0.6709		0.94 [ 0.90 ; 0.99 ]
Female		0.77 ( 0.84 . 0.02 )
NCI 2 MDA		0.85 0.83 1.08 1 1.03 1 1.03 1 0.75 1.43 1
IARC GWAS IARC Replication		0.88 0.81 0.97 1.14 0.98 1.32
Combined Heterogeneity P-value= 0.0111	◆	0.93 [ 0.87 , 0.99 ]
Overall Heterogeneity P-value= 0.6981	◆	0.94 [ 0.90 , 0.97 ]
Smoking		
NCI 1 NCI 2		0.86[0.70, 1.06] 1.02[0.87, 1.19]
MDA IARC GWAS		0.99 0.78 1.27 1 0.87 0.79 0.96 1
Combined Heterogeneity P-value= 0.081	▲	0.95 [ 0.89 ] 1.01 ]
Former		
NCI 1 NCI 2 MDA		0.79 0.86 0.95 0.84
IARC GWAS		0.90 0.79 1.02
Combined Heterogeneity P-value= 0.0583	◆	0.86 [ 0.80 ] 0.93 ]
Current NCI 1		1.06[0.87 1.28]
NCI 2 MDA		0.89 0.66 1.19 1.09 0.68 1.73
IARC GWAS IARC Replication		0.99 0.88 1.13 1.10 0.92 1.31
Heterogeneity P-value= 0.7482		1.02[0.04],1.11]
Overall Heterogeneity P-value= 0.013	◆	0.94 [ 0.90 , 0.98 ]
	0.50 1.00 1.50 2.00	

Odds Ratio



Odds Ratio





Odds Ratio

Body Mass Index BMI 15-24 NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.609		$\begin{array}{c} 1.17 & [0.91 & 1.50] \\ 1.05 & [0.81 & 1.36] \\ 1.62 & [1.00 & 2.62] \\ 1.13 & [0.98 & 1.30] \\ 1.21 & [0.98 & 1.36] \\ 1.21 & [0.96 & 1.52] \\ 1.15 & [1.05 & 1.27] \end{array}$
BML25-22 NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.7404		1.08 [ 0.88 . 1.30 ] 1.15 [ 0.91 . 1.44 1.07 [ 0.73 . 1.66 1.19 [ 1.06 . 1.35 1.05 [ 0.88 . 1.25 1.13 [ 1.04 . 1.22 ]
BMI 30-50 NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.6862		1.18 0.92 1.53 1.24 0.85 1.62 1.24 0.83 1.87 1.00 0.83 1.30 1.00 0.83 1.22 1.11 1.00 1.24
Combined Heterogeneity P-value= 0.8877	◆	1.13[1.07,1.19]
Hypertension No History NCI 1 NCI 2 MDA HARC GWAS IARC Replication Combined Heterogeneity P-value= 0.7822		$\begin{array}{c} 1.141 \\ 0.055 \\ 1.261 \\$
History NCI 1 NCI 2 MDA VARC Replication Combined Heterogeneity P-value= 0.421		1.09 [0.88 1.34] 1.16 [0.98 1.142] 1.44 [1.05 1.96 1.09 [0.93 1.28] 1.00 [0.79 1.26] 1.12 [1.02 1.23] 1.14 [1.07 1.21]
Sev		
Male NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.3361		1.15 [ 0.98 . 1.35 1.21 [ 1.08 . 1.37 1.50 [ 1.15 . 1.96 1.13 1 103 . 1.24 1.13 1 0.3 1.24 1.13 1 0.88 . 1.29 1.17 [ 1.10 . 1.24 ]
Female NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.979		1.10 0.87 1.38 1.06 0.99 1.25 1.06 0.75 1.59 1.11 0.09 1.25 1.05 0.88 1.26 1.09 1.09 1.17
Overall Heterogeneity P-value= 0.1433	◆	1.14 [ 1.09 , 1.19 ]
Smoking Never NCT MDA LARC GWAS LARC Replication Combined Heterogeneity P-value= 0.5465		1.24 [ 0.96 , 1.60 ] 1.13 [ 0.93 , 1.38 ] 1.23 [ 0.88 , 1.70 ] 1.14 [ 1.01 , 1.28 ] 0.96 [ 0.84 , 1.17 ] 1.11 [ 1.03 , 1.21 ]
Former NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.7472		1.03 [0.83, 1.27] 1.06 [0.84, 1.33] 1.31 [0.04, 1.83] 1.09 [0.93, 1.28] 1.00 [0.79, 1.26] 1.07 [0.97, 1.18]
Current NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.5636		1.17 [0.92, 1.50] 1.08 [0.73, 1.59 1.93 [1.06, 3.51] 1.77 [1.00, 1.36] 1.25 [1.01, 1.53] 1.20 [1.08, 1.33]
Overall Heterogeneity P-value= 0.2921	0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00	1.12 [ 1.08 , 1.18 ]

Odds Ratio





Odds Ratio

Body Mass Index BMI 15-24 NCI 1 NCI 2 MDA LARC Replication Combined Heterogeneity P-value= 0.1343 BMI 25-20		11 [0.60, 2.06] 77 [0.99, 3.19] 70 [1.31, 10.44] 74 [1.14, 2.67] 81 [0.37, 1.75] 54 [1.17, 2.02]
NCI 2 NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.4365		27 [ 0.78 , 2.06] 71 [ 1.02 , 2.87 72 [ 0.28 , 1.84 47 [ 1.03 , 2.10 80 [ 1.17 , 2.78 .48 [ 1.20 , 1.83 ]
BM 30-50 NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.8185		14 [0.60, 2.19] 36 [0.69, 2.67] 39 [0.30, 2.85] 90 [0.55, 1.47] 34 [0.74, 2.45] .11 [0.84, 1.48]
Combined Heterogeneity P-value= 0.2001	•	.39 [ 1.21 , 1.61 ]
Hypertension No History NCI 2 MDA UARC GWAS UARC Replication Combined Heterogeneity P-value= 0.8352		30 [ 0.86 , 1.98 ] 62 [ 1.16 , 2.25 ] 10 [ 0.54 , 2.24 ] 63 [ 0.98 , 2.69 ] 41 [ 0.73 , 2.73 ] 46 [ 1.19 , 1.80 ]
History NCI 1 NCI 2 MDA ARC SWAS IARC Replication Combined Heterogeneity P-value= 0.6667		13 [0.66 , 1.92] 61 [1.01 , 2.57] 76 [0.86 , 3.61] 40 [0.90 , 2.17] 01 [0.54 , 1.88] .36 [1.07 , 1.72]
Heterogeneity P-value= 0.6537	<b>▼</b>	.42[1.21,1.00]
Sex Male NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.472		97 [ 0.65 , 1.44 ] 31 [ 0.97 , 1.75 ] 33 [ 0.73 , 2.43 ] 46 [ 1.12 , 1.91 ] 55 [ 1.04 , 2.31 ] .33 [ 1.14 , 1.56 ]
Female NC11 NC12 MDA MDA KARC Replication Combined Heterogeneity P-value= 0.1456		77 [ 0.98 , 3.18 ] 59 [ 1.67 , 4.01 ] 88 [ 0.76 , 4.65 ] 36 [ 1.00 , 1.84 ] 29 [ 0.83 , 2.03 ] .61 [ 1.32 , 1.97 ]
Overall Heterogeneity P-value= 0.1407	• 1	.43 [ 1.27 , 1.62 ]
Smoking Never NCI T NCI 2 ARC GWAS IARC Replication Combined Heterogeneity P-value= 0.7728		44 [0.79, 2.64] 76 [1.15, 2.67] 65 [0.68, 4.01] 26 [0.89, 1.78] 65 [1.08, 2.53] 50 [1.22, 1.84]
Former NCI 7 NCI 2 MDA LARC GWAS LARC Replication Combined Heterogeneity P-value= 0.4675		88 [0.52 , 1.49] 84 [0.94 , 2.86] 51 [0.72 , 3.18] 40 [0.90 , 2.17] 01 [0.54 , 1.88] .25 [0.98 , 1.60]
Current NCI 1 NCI 2 MDA LARC GWAS LARC Replication Combined Heterogeneity P-value= 0.9235		27 [ 0.67 , 2.39 ] 16 [ 0.36 , 3.78 ] 03 [ 0.38 , 2.77 ] 63 [ 0.98 , 2.69 ] 41 [ 0.73 , 2.73 ] .39 [ 1.02 , 1.89 ]
Overall Heterogeneity P-value= 0.5375	1	.39 [ 1.21 , 1.60 ]
	0.00 2.00 4.00 6.00 8.00 10.00 12.00 Odds Ratio	







Body Mass Index BMI 15-24 BMI 15-24 NC1 2 NC1 2 NC2 2 IARC Replication Combined ARC Replication Combined Meterogeneity P-value= 0.2999 BMI 25-29 NC1 2 NC1 2 NC1 2 NC2 2 MDA IARC GWAS IARC GWAS IARC GWAS	$\begin{array}{c}1.15\\1.34\\1.02\\1.73\\1.14\\2.65\\1.74\\1.14\\2.45\\1.02\\1.16\\1.16\\1.16\\1.16\\1.16\\1.16\\1.16\\1.1$
Combined Meterogeneity P-value= 0.1858 BM 30-1 NC1 2 MDA JARC GWAS JARC GWAS JARC Replication Combined Heterogeneity P-value= 0.2109 Combined Heterogeneity P-value= 0.263	1.18 [ 1.10 ; 1.27 ] 1.18 [ 0.033 .1.44 ] 0.96 [ 0.78 ; 1.26 ] 1.01 [ 0.73 .1.40 ] 1.32 [ 1.13 .1.53 ] 1.26 [ 1.10 ; 1.32 ] 1.22 [ 1.16 , 1.28 ]
Hypertension No History NCT T NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.4402	$\begin{array}{c} 1.09 \\ 1.16 \\ 1.16 \\ 0.98 \\ 0.77 \\ 1.23 \\ 1.23 \\ 1.07 \\ 1.42 \\ 1.24 \\ 1.07 \\ 1.16 \\ 1.07 \\ 1.23 \\ 1.07 \\ 1.23 \\ 1.07 \\ 1.23 \\ 1.07 \\ 1.23 \\ 1.07 \\ 1.23 \\ 1.07 \\ 1.23 \\ 1.07 \\ 1.23 \\ 1.07 \\ 1.23 \\ 1.07 \\ 1.23 \\ 1.07 \\ 1.23 \\ 1.07 \\ 1.23 \\ 1.07 \\ 1.23 \\ 1.07 \\ 1.23 \\ 1.07 \\ 1.$
History NCT NCT MDA ARC Replication Combined Heterogeneity P-value= 0.3187 Qvgrall	1.31 [ 1.10, 1.58] 1.08 [ 0.83, 1.27] 1.08 [ 0.84, 1.40] 1.08 [ 0.84, 1.40] 1.25 [ 1.00, 2, 1.21] 1.14 [ 1.05, 1.23] 1.14 [ 1.09, 1.21]
Sex Male NCI 1 NCI 2 MDA IARC Replication Combined Heterogeneity P-value= 0.211	1.10 [0.96, 1.26] 0.94 [0.77, 1.26] 1.14 [1.02, 1.26] 1.06 [1.02, 1.20] 1.25 [1.10, 1.41] 1.25 [1.10, 1.16]
Female NCI 1 NCI 2 MDA JARC GWAS JARC Replication Combined Heterogeneity P-value= 0.0119 QVErall	1.35 [ 1.11 , 1.64 1.08 (0.93 , 1.25) 1.37 [ 0.98 , 1.92 ] 1.47 [ 1.33 , 1.63] 1.43 [ 1.22 , 1.68] 1.35 [ 1.26 , 1.45] 1.20 [ 1.15 , 1.25]
Smoking Smoking NCT NCT NCT NCT NCT NCT NCT NCT NCT NCT	1.33 [ 1.07, 1.64 ] 0.68 [ 0.83, 1.17 ] 1.01 [ 0.78 : 1.30 ] 1.37 [ 1.24 : 1.52 ] 1.37 [ 1.18 : 1.36 ]
Former NCI 1 MDA JARC GWAS JARC Replication Combined Heterogeneity P-value= 0.408	1.07 [0.89, 1.29] 1.30 [1.07, 1.58] 1.13 [0.85, 1.49] 1.05 [0.92] 1.21 1.25 [1.00, 1.55] 1.14 [1.04, 1.24]
Current NCI 1 NCI 2 MDA JARC GWAS JARC Replication Combined Heterogeneity P-value= 0.7239	1.17 [0.94, 1.46] 0.98 [0.71, 1.36] 1.04 [0.66, 1.64] 1.23 [1.07, 1.42] 1.24 [1.03, 1.50] 1.19 [1.08, 1.31]

٦

3.00

Т

2.50

1.21 [ 1.15 , 1.27 ]

Γ

0.50

1.00

1.50

Odds Ratio

2.00

Overall Heterogeneity P-value= 0.1338

Body Mass Index BMI 15-24		
NCI 2		1.16 0.93 . 1.44
MDA IARC GWAS		1.54 1.02 2.34 1.20 1.06 1.37
IARC Replication Combined		1.51 [ 1.23 ] 1.85 1.30 [ 1.19 ] 1.42 ]
Heterogeneity P-value= 0.1585		
NCI 1	<b>⊢−</b> −−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−	1-28 [ 1-08 - 1-53 ]
MDA MDA		0.76 0.56 1.02
IARC Replication		1.17 1.00 . 1.38
Heterogeneity P-value= 0.0408	•	1.19[1.11,1.28]
<u> RMI 30-50</u>		1 17 [ 0.04 1 48 ]
NCI 2	, <del>                                     </del>	1.03 0.81 1.30
IARC GWAS		1.29 [ 1.11 . 1.50 ]
Combined Heterogeneity P-values 0 3278	◆	1.19 [ 1.09 ] 1.31 ]
Combined	•	1 22 [ 1 17 1 28 ]
Heterogeneity P-value= 0.2743	•	1.22[1.17,1.20]
Hypertension No History		
NCI 1		1.20 [ 1.03 . 1.39 ]
MDA IARC GWAS		
IARC Replication Combined		1.30 1.07 1.581 1.18 1.10 1.271
Heterogeneity P-value= 0.1816	<b>•</b>	
History NCL1		1.25[1.04, 1.50]
NCI 2 MDA		1.17 1.00 1.371
IARC GWAS IARC Replication		1.10 0.95 1.27 1 1.15 0.92 1.44 1
Combined Heterogeneity P-value= 0.7874	· · · · · · · · · · · · · · · · · · ·	1.15 [ 1.06 ] 1.24 ]
Qverall	•	1.16[1.10.1.23]
Héférőgeneity P-value= 0.6162	•	
Sex Male		
NCI 1 NCI 2		1.13 [ 0.98 , 1.30 ] 1.18 [ 1.06 , 1.31 ]
MDA IARC GWAS		0.88 [ 0.72 ] 1.08 ] 1.11 [ 1.03 ] 1.21 ]
ARC Replication		1.20 [ 1.06 , 1.37 ] 1.13 [ 1.07 , 1.19 ]
Heterogeneity P-value= 0.1286	-	
NCI 1	<b>⊢</b> ∎1	1-39[1-14-1-70]
MDA		1.33 [ 0.95 ] 1.88 ]
IARC GWAS IARC Replication		1.42 1.29 1.58 1.45 1.24 1.70
Heterogeneity P-value= 0.1814	◆	1.30[1.27, 1.40]
Qverall	◆	1.21 [ 1.16 , 1.26 ]
Smoking		
Never		122[108 184]
NCI 2		1.05 0.88 1.25
ARC GWAS		1.36 1.22 1.51
Combined Hetergeneity P-value= 0.0174	•	1.26 [ 1.17 ] 1.35 ]
Former		
NCI 2	ŀ÷_∎l	1.14 [ 0.95 . 1.38 ]
MDA IABC GWAS		1.10 0.83 1.45
ARC Replication		1.15 0.02 1.1.44
Heterogeneity P-value= 0.5216	-	1.10[1.07,1.27]
Current NCL1		1 17 [ 0 04 1 45 ]
NČI 2 MDA		1.02 0.73 1.411
IARC GWAS IARC Replication		1.15 1.00 1.33
Combined Heterogeneity P-value= 0.6692	◆	1.17 [ 1.06 , 1.28 ]
Overall	•	1.21 [ 1.15 , 1.26 ]
Heterogeneity P-value= 0.2676		
	0.50 1.00 1.50 2.00 2.50	
	Odda Batia	
	COUS RAID	





Odds Ratio

Body Mass Index		
BMI 15-24 NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.7481		$\begin{array}{c} 1.10 & [ & 0.90 & . & 1.33 \\ 0.04 & [ & 0.76 & . & 1.15 \\ 0.05 & [ & 0.68 & . & 1.33 \\ 1.05 & [ & 0.44 & . & 1.18 \\ 0.97 & [ & 0.81 & . & 1.17 \\ 1.02 & [ & 0.95 & . & 1.10 \\ \end{array}$
BMI 25-29 NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.0796		1.18 [ 1.00, 1.36 ] 1.22 [ 1.02, 1.46 ] 1.23 [ 0.22, 1.46 ] 0.67 [ 0.88 , 1.07 ] 1.05 [ 0.91 , 1.22 ] 1.06 [ 1.00 , 1.14 ]
BMI 30-50 NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.0768		0.99 [0.82, 1.20] 1.31 [1.06, 1.63] 0.97 [0.71, 1.33] 1.17 [1.02, 1.34] 0.94 [0.80, 1.11] 1.08 [1.00, 1.17]
Combined Heterogeneity P-value= 0.5997	◆	1.06 [ 1.01 , 1.10 ]
Hypertension No History NCI 1 NDA MRC GWAS IARC Replication Combined Heterogeneity P-value= 0.8036		$\begin{array}{c} 1.04 & \begin{bmatrix} 0.21 & 1.19 \\ 0.080 & 1.24 \\ 1.13 & 0.080 & 1.24 \\ 1.08 & 0.080 & 1.44 \\ 1.08 & 0.080 & 1.22 \\ 0.080 & 0.080 & 1.16 \\ 1.07 & \begin{bmatrix} 1.00 & 1.14 \\ 1.00 & 1.14 \end{bmatrix} \end{array}$
History NCI 1 NCI 2 MDA JARC GREDication Combined Combined Heterogeneity P-value= 0.7231		$\begin{array}{c} 1.18 \\ 1.07 \\ 0.92 \\ 1.23 \\ 1.08 \\ 0.95 \\ 1.03 \\ 0.94 \\ 1.17 \\ 1.33 \\ 0.94 \\ 1.37 \\ 1.09 \\ 1.01 \\ 1.$
Heterogeneity P-value= 0.6901	<b>•</b>	1.07 [ 1.02 , 1.15 ]
Male NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.6862		$\begin{array}{c} 1.16 \left[ 1.02 , 1.30 \right] \\ 1.10 \left[ 1.00 , 1.21 \right] \\ 1.11 \left[ 0.91 , 1.34 \right] \\ 1.04 \left[ 0.97 , 1.13 \right] \\ 1.06 \left[ 0.95 , 1.19 \right] \\ 1.08 \left[ 1.03 , 1.13 \right] \end{array}$
Female NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.1327		1.00 [0.83, 1.20] 1.15 [1.01, 1.32] 1.12 [0.83, 1.51] 1.07 [0.98, 1.17] 0.91 [0.79, 1.04] 1.05 [0.99, 1.11]
Overall Referogeneity P-value= 0.4444	◆	1.07 [ 1.03 , 1.11 ]
Smoking Netr NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.6224		$\begin{array}{c} 1.17 & \begin{bmatrix} 0.96 & 1.41 \\ 1.11 & 0.95 & 1.31 \\ 1.06 & 0.33 & 1.35 \\ 1.04 & 0.44 & 1.14 \\ 0.89 & 0.87 & 1.13 \\ 1.05 & \begin{bmatrix} 0.99 & 1.12 \\ 0.99 & 1.12 \end{bmatrix} \end{array}$
Former NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.4496		$\begin{array}{c} 1.09 \begin{bmatrix} 0.92 & 1.29 \\ 126 \begin{bmatrix} 1.05 & 1.51 \\ 127 \end{bmatrix} \\ 1.21 \begin{bmatrix} 0.93 & 1.59 \\ 1.31 \end{bmatrix} \\ \begin{array}{c} 0.91 & 1.17 \\ 1.31 \end{bmatrix} \\ \begin{array}{c} 0.94 & 1.37 \\ 1.11 \begin{bmatrix} 1.03 & 1.20 \end{bmatrix} \end{array}$
Current NCI 1 NCI 2 MDA IARC GWAS IARC Replication Combined Heterogeneity P-value= 0.7134		1.04 [0.87, 1.25] 0.88 [0.66, 1.19] 0.92 [0.61, 1.39] 1.08 [0.95, 1.22] 0.98 [0.82, 1.16] 1.02 [0.94, 1.11]
Overall Heterogeneity P-value= 0.331	0.60 0.80 1.00 1.20 1.40 1.60 1.80	1.06 [ 1.02 , 1.11 ]

Odds Ratio

# Supplementary Tables.

# Supplementary Table 1. Description of the studies participating in the RCC GWAS meta-analysis.

	Designs		Genotyped Samples		Samples Used in Final Analysis		Genotypi	ng Array
Study Name (Abbreviation)	Location	Study Population	Cases	Controls	Cases	Controls	Cases	Controls
NEW SAMPLES			5,722	7,439	5,198	7,331		
IARC-2 scan								
The European Prospective Investigation into Cancer and Nutrition (EPIC)	Prospective cohort 10 European countries	Adults aged 35-74 enrolled between 1992 and 2000 (n=521,468) Incident cancers identified through health insurance records, cancer and pathology registries and active follow-up (subjects and next of skin) Genomic DNA extracted from buffy coat	127	138	127	138	Omni 5	Omni 5
CeRePP	Case series France	Pathologically confirmed RCC recruited through the CeRePP network. Controls recruited from a systematic urologic screening program, which includes men or women who had no history or symptoms of kidney. diseases and with a normal morphologic status of kidneys at ultrasonographi examination. Genomic DNA extracted from blood and saliva samples.	411 c	429	402	422	Omni 5	Omni 5
Umea	Prospective cohort Sweden	Population-based cohort, recruiting since 1985; resident from the Västerbotten county in northern Sweden. Incident cases identified through linkage to national death and cancer registries. Genomic DNA extracted from blood.	306	312	297	301	Omni 5	Omni 5
Karolinska	2 Prospective cohorts Sweden	COSM: Cohort of Swedish Men (45,306 men enrolled in 1997) and SMC: Swedish Mammography Cohort (61,433 women enrolled between 1987 and 1990), in central Sweden. Incident cases identified through linkage to national death and cancer registries. Genomic DNA extracted from saliva.	131	298	131	295	Omni 5	Omni 5
Consortium For the Investigation of Renal Malignancies/ Melbourne Collaborative Cohort Study (ConFIRM/MCCS)	Case-control and cohort studies; Australia	Incident cases diagnosed in Victoria and Queensland in the period 2011-2014 and aged 18-74 years (ConFIRM), and from within the MCCS when fresh blood collected; Controls selected from healthy participants in the MCCS cohort; Genomic DNA extracted from whole blood (ConFIRM) and buffy coat (MCCS).	188	398	184	396	Omni 5	Omni 5
The IARC K2 study	Case-control study 4 central/eastern Europe countries	Multicentric study conducted in 2007-2013 in Russia, Czech Republic, Romania, and Serbia. Hospital or population-based controls depending on recruiting centers.	1,675	1,458	1,640	1,388	Omni 5	Omni 5/ Omni Express
IARC-2 Scan Total			2,838	3,033	2,781	2,940		
NCI-2 Scan:								
Agricultural Health Study (AHS)	Prospective cohort; USA (Iowa, North Carolina)	Private and commercial pesticide applicators and spouses of private applicators, enrolled between 1993 and 1997 (n = 89,655). Incident cancers identified through linkage with state cancer registries. Germline DNA extracted from buccal cell samples.	78	-	7	-	Omni Express	-
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC)	Prospective cohort / randomized trial; Finland	Male smokers aged 50-69 at entry, enrolled between 1985 and 1988 (n = 29,133). Incident cancers identified through linkage to Finnish Cancer Registry. Germline DNA extracted from whole blood samples.	41	221*	39	221*	Omni Express	Omni 2.5

BioVU	Hospital biorepository; USA (Nashville)	Renal cancer patients treated at Vanderbilt University Medical Center between 2006 and 2012. Controls selected from among patients admitted for non-cancer condition, frequency matched by age and sex.	714	222	629	207	Omni Express	Omni Express
American Cancer Society Cancer Prevention Study II Nutrition Cohort (CPS-II)	Prospective cohort; USA	Men and women aged 50-74 at entry, enrolled between 1992 and 1993 (n = 184,194). Incident cancers identified from biannual follow-up questionnaires or linkage with state cancer registrics. Germline DNA extracted from blood and buccal cell samples.	85	212*	70	212*	Omni Express	Omni 2.5
Dana-Farber/Harvard Cancer Center (DFHCC)	Case series; USA (Boston)	Patients with localized renal cancer treated at DFHCC between 2002 and 2010. Genomic DNA extracted from blood samples.	234	-	206	-	Omni Express	-
Health Professionals Follow-up Study (HPFS)	Prospective cohort; USA	Men in selected health professions, enrolled in 1986 (n = 51,529). Incident cancers identified from follow-up questionnaires and subsequent medical record review. Germline DNA extracted from blood samples.	50	85*	38	85*	Omni Express	Omni Express
Nurses' Health Study (NHS)	Prospective cohort; USA	Female registered nurses aged 30-55, enrolled in 1976 (n = 121,700). Incident cancers identified by mailed follow-up questionnaire and subsequent medical record review. Germline DNA extracted from blood samples.	66	434 <sup>*</sup>	57	434*	Omni Express	Omni Express
Physicians Health Study (PHS)	Prospective cohort / randomized trial; USA	Male physicians aged 50+ enrolled between 1982 and 1984 ( $n = 22,071$ ). Incident cancers identified by mailed follow-up questionnaire. Germline DNA extracted from blood samples.	27	-	21	-	Omni Express	-
Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO)	Prospective cohort / cancer screening trial; USA	Men and women aged 55-74 at entry, enrolled between 1993 and 2001 ( $n = 155,000$ ). Incident cancers identified from annual questionnaires, with confirmation through medical records. Gemline DNA extracted from buffy coat and buccal cell samples.	118	3,003*	93	3,003*	Omni Express	Omni 2.5
Van Andel Research Institute (VARI)	Case series; USA	Renal cancer patients treated at the Spectrum Health Hospital in Grand Rapids, MI, and in hospitals affiliated with the Cooperative Human Tissue Network (CHTN). Germline DNA extracted from adjacent normal kidney tissue.	1,050	-	920	-	Omni Express	-
Vitamins and Lifestyle Study (VITAL)	Prospective cohort; USA (Washington State)	Men and women aged 50-76, enrolled between 2000 and 2002. Incident cancers identified by linkage to the western Washington SEER cancer registry. Germline DNA extracted from buccal cell samples.	112	-	91	-	Omni Express	-
Women's Health Initiative (WHI)	Prospective cohort / randomized trial; USA	Women aged 50-79, enrolled between 1993 and 1998. Incident cancers were identified by mailed follow-up questionnaires, and verified by medical records. Genomic DNA extracted from buffy coat samples.	300	229*	239	229*	Omni Express	Omni Express
Women's Health Study (WHS)	Prospective cohort / randomized trial; USA	Female health professionals aged 45 years or older, enrolled in 1993. Incident cancers identified by mailed follow-up questionnaire. Genomic DNA extracted from blood samples.	9	-	7	-	Omni Express	-
NCI-2 Scan Total			2,884	4,406	2,417	4,391		
PREVIOUSLY AVAILABLE SAMP	LES		6,031	13,436	5,585	13,075		
IARC-1 scan								

The European Prospective	Prospective cohort	Adults aged 35-74 enrolled between 1992 and 2000 (n=521,468)	319	434	275	414	610Q	550K
Investigation into Cancer and	10 European countries	Incident cancers identified through health insurance records, cancer and						
Nutrition (EPIC) pathology registries and active follow-up (subjects and next of skin)								
[additional to above]		Genomic DNA extracted from buffy coat						

The Nord-Trøndelag Health (HUNT2) and Tromsø Studies (Tromsø IV)	2 Prospective cohorts Norway	HUNT2: Adults aged 20+ enrolled between 1995 and 1997 (N=65,285) Tromsø IV: Adults aged 25+ enrolled between 1994-1995 (N=27,158) Cases identified through Norwegian Cancer Registries Genomic DNA extracted from buffy coat		433	133	388	610Q	317K
The NCI/IARC study in central Europe (CE)	Case-control study 4 European countries	Hospital based study conducted between 1999-2003 (except Poland) 2004-2007 (Poland). Controls matched to lung cancer and included in previous GWAS of lung cancer Genomic DNA extracted from buffy coat and RBC	1,152	2,179	1,096	2,058	317K	317K
Arsenic Health Risk Assessment and Molecular Epidemiology study in Central Europe (ASHRAM)	Case-control study Slovakia and Hungary	Cases recruited in 6 counties between 2002-2004 Controls matched to lung cancer and included in previous GWAS of lung cancer Genomic DNA extracted from whole blood	89	425	84	399	610Q	317K
CeRePP [additional to above]	Case series France	Pathologically confirmed RCC involved in PROGENE-CeRePP cohort French controls originally participated in a hospital based case-control study of UADT cancer Genomic DNA extracted from blood	79	166	58	146	610Q	317K
The Leeds cohort	Case series UK	RCC from the Leeds cohort recruited between 1998-2007 Genomic DNA extracted from blood	363	-	348	-	610Q	-
SEARCH Kidney cancer study (SEARCH)	Case series UK	Population based case series including all patients with a kidney cancer aged 70- and diagnosed between 2002-2006 Genomic DNA extracted from blood	187	-	181	-	610Q	-
WTCCC	Controls UK	Dataset generated by the Wellcome Trust Sanger Institute in collaboration with the 1958 Birth cohort Genomic DNA extracted from blood	-	1,438	-	1,361	-	550K
Moscow	Case-control study Moscow	Incident cases were recruited between 2007-2009. Hospital based controls were match and recruited during same period Genomic DNA extracted from blood	305	323	263	305	610Q	610Q
IARC -1 Scan Total			2,639	5,398	2,438	5,071		
NCI-1 Scan:								
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC)	See above	See above	177	1,288*	163	1,288*	660W	610K
American Cancer Society Cancer Prevention Study II Nutrition Cohort (CPS-II)	See above	See above	226	730 <sup>*</sup>	202	730 <sup>*</sup>	660W	610K
Prostate, Lung, Colorectal and								
(PLCO)	See above	See above	330	845*	284	845*	660W	550/610K
(PLCO) National Cancer Institute U.S. Kidney Cancer Study (USKC)	See above Case-control; USA (Chicago, Detroit)	See above Cases: 1,227 men and women aged 20-79 at diagnoses, identified from Chicago hospital records and Metropolitan Detroit Cancer Surveillance System between 2003 and 2007. Controls: 1,235 men and women recruited from state Department of Motor Vehicle records (ages 30-64) and Medicare beneficiary records (ages 65+), frequency matched to cases on age, race, sex, region. Genomic DNA extracted from blood and buccal cell samples.	330 720	845* 595	284 662	845° 561	660W 610K	550/610K 610K

MD Anderson Scan:	Case-control; USA (Texas)	Cases: 894 Caucasian men and women treated for renal cancer at the University of Texas MD Anderson Cancer Center. Controls:556 Caucasian men and women identified through random-digit dialing. Genomic DNA extracted from blood samples.	894	556	893	556	660W	660W
<u>UK Scan:</u>	Case series; UK	Cases: adult renal cancer patients identified from UK clinical oncology centers and the Institute of Cancer Research and Royal Marsden NHS Hospitals Trust. Controls: previously genotyped samples from the Wellcome Trust Case Control Consortium 2 1958 birth cohort and UK Blood Service Control Group (WTCC controls included in the IARC-1 scan were excluded). Genomic DNA extracted from blood samples.	1,045	4,024 <sup>*</sup>	944	4,024 <sup>°</sup>	Omni Express	Hap 1.2M Duo

\*Previously scanned controls

		Previously Reported GWAS				Current Meta-Analysis				
SNP	Locus	Study	OR	(95% CI)	Р	OR	(95% CI)	Р	<b>P</b> <sub>Heterogeneity</sub>	MAF
rs3845536	1q24.1	Henrion et al. <sup>1</sup>	1.21	(1.13-1.30)	2.3 x 10 <sup>-8</sup>	1.05	(1.01-1.09)	0.0062	3.0 x 10 <sup>-5</sup>	0.36
rs7579899	2p21	Purdue et al. <sup>2</sup>	1.15	(1.10-1.21)	2.3 x 10 <sup>-9</sup>	1.15	(1.11 - 1.20)	5.3 x 10 <sup>-15</sup>	0.31	0.49
rs11894252	2p21	Purdue et al. <sup>2</sup>	1.14	(1.09-1.20)	1.8 x 10 <sup>-8</sup>	1.16	(1.12 - 1.20)	2.7 x 10 <sup>-15</sup>	0.28	0.49
rs12105918	2q22.3	Henrion et al. <sup>3</sup>	1.29	(1.18 - 1.41)	1.8 x 10 <sup>-8</sup>	1.25	(1.16 - 1.34)	3.9 x 10 <sup>-9</sup>	0.14	0.06
rs35252396*	8q24	Gudmundsson et al. <sup>4</sup>	1.27	(1.18 - 1.37)	5.4 x 10 <sup>-11</sup>	1.13	(1.10 - 1.18)	2.8 x 10 <sup>-12</sup>	0.17	0.44
rs7105934	11q13	Purdue et al. <sup>2</sup>	0.69	(0.62 - 0.76)	7.8 x 10 <sup>-14</sup>	0.70	(0.65 - 0.75)	4.9 x 10 <sup>-22</sup>	0.20	0.08
rs718314	12p11.23	Wu et al. <sup>5</sup>	1.19	(1.13-1.26)	8.9 x 10 <sup>-10</sup>	1.18	(1.14 - 1.23)	2.2 x 10 <sup>-16</sup>	0.45	0.26
rs1049380	12p11.23	Wu et al. <sup>5</sup>	1.18	(1.12 - 1.25)	6.1 x 10 <sup>-9</sup>	1.15	(1.11 - 1.19)	2.0 x 10 <sup>-12</sup>	0.02	0.44
rs4765623	12q24	Purdue et al. <sup>2</sup>	1.15	(1.09-1.20)	2.6 x 10 <sup>-8</sup>	1.14	(1.10-1.18)	2.8 x 10 <sup>-12</sup>	0.22	0.34

### Supplementary Table 2. Meta-analysis results for previously reported RCC GWAS loci

ORs computed for minor allele vs. common allele. \*Current meta-analysis based on rs64070588, in complete LD with rs35252396.

Supplementary Table 3. Description of the studies included in replication stage.

	D '	Genotyped Samples			
Study Name (Abbreviation)	Design; Location	Study Population	Cases	Controls	
IARC Replication	Case-control and cohort studies; Europe and Australia	The sample set was composed of additional cases and controls selected from the following studies described in Supp table 1: IARC K2, CE, Umea, and ConFIRM/MCCS	1,674	4,222	
Mayo Clinic (Mayo)	Case-control; USA	Cases: Caucasian men and women treated for RCC at Mayo. Controls: patients admitted to General Medicine Clinics at Mayo	909	1,479	
MD Anderson (MDA)	Case-control; Houston, USA	Cases: Caucasian men and women treated for renal cancer at MDA. Controls: Caucasian men and women identified through random-digit dialing. (additional samples to these described in Supp table 1).	599	600	

	IARC-1/2		NCI-2	
		Pearson		Pearson
	A	correlation	A /	correlation
SNP	% concordance	coefficient (r <sup>2</sup> )	% concordance	coefficient (r <sup>2</sup> )
rs10936602 <sup>a</sup>	99.6	0.995	100.00	1.000
rs11637556°	99.8	0.998	100.00	0.999
rs11813268°	97.8	0.958	99.82	0.994
rs1266819°	99.7	0.997	99.82	0.996
rs13376700 <sup>°</sup>	99.7	0.997	99.46	0.985
rs17050872 <sup>a</sup>	98.3	0.979	100.00	1.000
rs1800057 <sup>b</sup>	98.8	0.824	98.89	0.817
rs2109794 <sup>b</sup>	99.3	0.990	99.81	0.989
rs2203002 <sup>a</sup>	99.3	0.971	99.05	0.878
rs2241261 <sup>a</sup>	99.6	0.995		
rs234043 <sup>a</sup>	99.2	0.990	99.82	0.996
rs2889 <sup>a</sup>	99.1	0.990	99.64	0.991
rs4381241 <sup>a</sup>	99.7	0.997	99.82	0.991
rs4662750 <sup>ª</sup>	97.0	0.967	97.90	0.909
rs4804368 <sup>a</sup>	99.8	0.997	99.82	0.993
rs4903064 <sup>a</sup>	98.9	0.985	99.05	0.948
rs59294613 <sup>b</sup>	99.9	0.999	100.00	1.000
rs6706003 <sup>b</sup>	98.1	0.980	98.23	0.944
rs67311347 <sup>b</sup>	98.9	0.985	98.68	0.863
rs6755594 <sup>b</sup>	98.1	0.979	99.26	0.967
rs714024 <sup>b</sup>	98.8	0.986	98.64	0.926
rs72730336 <sup>b</sup>	99.8	0.997	99.82	0.991
rs72851889 <sup>b</sup>	97.0	0.781	96.29	0.591
rs72855540 <sup>b</sup>	99.1	0.933	98.85	0.825
rs73149977 <sup>a</sup>	99.4	0.992	99.82	0.992
rs74911261 <sup>a</sup>	99.3	0.905	99.63	0.899
rs76912165 <sup>b</sup>	96.6	0.851	96.61	0.491
rs7697932 <sup>b</sup>	99.1	0.990	98.57	0.906
rs77736197 <sup>a</sup>	99.7	0.985	99.25	0.895
rs77774900 <sup>a</sup>	99.0	0.970	99.42	0.906
rs7913447 <sup>b</sup>	98.3	0.980	98.85	0.941
rs8007348 <sup>b</sup>	99.8	0.997	100.00	1.000

Supplementary Table 4. Technical validation of top SNPs; concordance rates between genome-wide-scanned or imputed SNPs and Taqman genotyping.

<sup>a</sup>Imputed or genotyped across scans; <sup>b</sup>imputed across all scans.

Analysis	OR	95% CI	Р
All RCC			
Across PRS deciles			
1	1.00		
2	1.34	(1.16-1.54)	3.60E-05
3	1.41	(1.23-1.62)	8.30E-07
4	1.56	(1.36-1.79)	1.00E-10
5	1.71	(1.50-1.96)	1.98E-15
6	1.93	(1.69-2.20)	8.40E-23
7	1.93	(1.69-2.20)	7.20E-23
8	2.11	(1.85-2.40)	1.20E-29
9	2.52	(2.22-2.86)	8.40E-46
10	3.24	(2.86-3.67)	1.20E-76
Continuous (per PRS unit increase)	2.85	(2.62-3.11)	2.30E-125
By histology (per PRS unit increase)			
Clear cell RCC vs. controls	3.24	(2.91-3.62)	3.40E-100
Papillary RCC vs. controls	1.83	(1.44-2.32)	5.30E-07
Chromophobe RCC vs. controls	2.34	(1.58-3.46)	2.40E-05
By RCC age at onset (per PRS unit increased	se)		
<60 vs. 60+	1.01	(0.88-1.15)	9.10E-01
By stage (per PRS unit increase)			
2 vs. 1	0.92	(0.63-1.36)	6.90E-01
3 vs. 1	1.24	(0.91-1.70)	1.80E-01
4 vs. 1	1.36	(0.97 - 1.93)	8.00E-02

# Supplementary Table 5. Associations with 13-SNP RCC polygenic risk score (PRS): overall, and by histology, age at onset and stage

#### **Supplementary Note**

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https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigato r %20Long%20List.pdf".

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