Supplementary Table 1. Comparison of demographic characteristics of patients with RCC and control subjects

Characteristic	Cases n=577	Control n=593	P value
Age (years)			
Mean (SD)	59.3 (10.7)	58.9 (9.3)	0.524
Sex, n(%)			
Men	382 (66.20)	382 (64.42)	
Women	195 (33.80)	211 (35.58)	0.521
Smoking status, n(%) *			
Never smoker	305 (52.95)	294 (49.58)	
Former smoker	200 (34.72)	212 (35.75)	
Current smoker or recent quitter	71 (12.33)	87 (14.67)	0.382
Pack-years smoking			
Median (range)	19 (0.15-150)	24 (0.05-133)	0.195
Hypertension			
Yes	325 (56.42)	240 (40.47)	
No	251 (43.58)	353 (59.53)	<0.001
Usual BMI †			
Normal (<25 kg/m^2)	80 (17.20)	161 (27.52)	
Overweight (25-29.9 kg/m^2)	178 (38.28)	223 (38.12)	
Obese (≥30 kg/m^2)	207 (44.52)	201 (34.36)	<0.001
Continuous, Mean(SD)	30.7 (7.23)	28.7 (6.06)	<0.001
BMI at age 20			
Normal (<25 kg/m^2)	304 (65.80)	446 (76.24)	
Overweight (25-29.9 kg/m^2)	124 (26.84)	118 (20.17)	
Obese (≥30 kg/m^2)	34 (7.36)	21 (3.59)	<0.001
Continuous, Mean(SD)	23.9 (4.20)	22.7 (3.63)	<0.001
BMI at age 40			
Normal (<25 kg/m^2)	145 (32.44)	265 (46.49)	
Overweight (25-29.9 kg/m^2)	180 (40.27)	220 (38.60)	
Obese (≥30 kg/m^2)	122 (27.29)	85 (14.91)	<0.001
Continuous, Mean(SD)	27.9 (5.83)	25.9 (4.81)	<0.001
Physical activity ‡			
Intensive	77 (17.04)	214 (36.96)	
Medium	124 (27.43)	200 (34.54)	
Low	251 (55.53)	165 (28.50)	<0.001

*Smoking status: Never smoker, individuals who had never smoked or had smoked <100 cigarettes in their life time; Former smoker, individuals who had smoked at least 100 cigarettes in their lifetime but had quit more than 12 months before recruitment; Current smokers, individuals who are currently smoking or had quit less than 12 months before recruitment.

†Usual BMI refers to BMI at 3yrs before the diagnosis or recruitment.

‡ Intensive: MET≥45/wk.; Medium: MET 27-44.9/wk.; Low: MET<27/wk.

Supplementary Table 2. The comparison of characteristics for cases with genotyping data and those without

Characteristics	Cases with genotyping data	Cases without genotyping data	p-value
N=577	402 (69.67%)	175(30.33%)	
Age, Mean(SD)	59.7(10.4)	58.3(11.3)	0.136
Sex			
Male	272(67.66%)	110(62.86%)	0.262
Female	130(32.34%)	65(37.14%)	
Smoking *			
Non-smokers	200(49.88%)	105(60.00%)	0.065
Former smokers	153(38.15%)	47(26.86%)	
Recent quitters	13(3.24%)	5(2.86%)	
Current smokers	35(8.73%)	18(10.29%)	
Usual BMI †			
Normal (<25 kg/m^2)	60(16.90%)	20(18.18%)	0.178
Overweight (25-29.9 kg/m^2)	144(40.56%)	34(30.91%)	
Obese (≥30 kg/m^2)	151(42.54%)	56(50.91%)	
BMI at age 40			
Normal (<25 kg/m^2)	111(32.55%)	33(31.73%)	0.497
Overweight (25-29.9 kg/m^2)	141(41.35%)	38(36.54%)	
Obese (≥30 kg/m^2)	89(26.10%)	33(31.73%)	
BMI at age 20			
Normal (<25 kg/m^2)	231(65.44%)	73(66.97%)	0.054
Overweight (25-29.9 kg/m^2)	101(28.61%)	23(21.10%)	
Obese (≥30 kg/m^2)	21(5.95%)	13(11.93%)	
Weight change			
Weight loss >0 lbs.	15(4.41%)	9(8.74%)	0.286
Weight gain 0.1-10 lbs.	85(25.00%)	23(23.33%)	
Weight gain 10.1-25 lbs.	109(32.06%)	28(27.18%)	
Weight gain >25 lbs.	131(38.53%)	43(41.75%)	
Physical activity ‡			
Intensive	61(17.63%)	16(15.09%)	0.790
Medium	93(26.88%)	31(29.25%)	
Low	192(55.49%)	59(55.66%)	
Hypertension			
No	168(41.79%)	83(47.70%)	0.189
Yes	234(58.21%)	91(52.30%)	

*Smoking status: Never smoker, individuals who had never smoked or had smoked <100 cigarettes in their life time; Former smoker, individuals who had smoked at least 100 cigarettes in their lifetime but had quit more than 12 months before recruitment; Current smokers, individuals who are currently smoking or had quit less than 12 months before recruitment.

†Usual BMI refers to BMI at 3yrs before the diagnosis or recruitment.

‡ Intensive: MET≥45/wk.; Medium: MET 27-44.9/wk.; Low: MET<27/wk.

Supplementary Table 3. Comparison of host characteristics across weight change groups

Characteristics	Weight loss >0 lbs.	Weight gain 0.1-10 lbs.	Weight gain 10.1-25 lbs.	Weight gain >25 lbs.	p-value
Case/Control	24/28	109/204	138/167	174/171	
Age, Mean(SD)	59.1(8.9)	61.5(9.1)	60.3(8.9)	57.6(9.3)	<0.001
Age, Median(Range)	59(41-81)	62(40-86)	61(41-87)	58(40-78)	<0.001
Sex					
Male	34(65.38%)	196(62.62%)	207(67.87%)	231(66.96%)	
Female	18(34.62%)	117(37.38%)	98(32.13%)	114(33.04%)	0.533
Smoking *					
Non-smokers	23(44.23%)	147(47.12%)	166(54.43%)	170(49.28%)	0.199
Former smokers	19(36.54%)	124(39.74%)	103(33.77%)	125(36.23%)	
Recent quitters	0(0.00)	4(1.28%)	7(2.3%)	12(3.48%)	
Current smokers	10(19.23%)	37(11.86%)	29(9.51%)	38(11.01%)	
Usual BMI †					
Normal (<25 kg/m^2)	15(28.85%)	127(40.58%)	63(20.72%)	25(7.25%)	<0.001
Overweight (25-29.9 kg/m^2)	22(42.31%)	129(41.21%)	139(45.72%)	103(29.86%)	
Obese (≥30 kg/m^2)	15(28.85%)	57(18.21%)	102(33.55%)	217(62.90%)	
BMI at age 40					
Normal (<25 kg/m^2)	22(42.31%)	207(66.13%)	133(43.61%)	48(13.91%)	<0.001
Overweight (25-29.9 kg/m^2)	23(44.23%)	91(29.07%)	146(47.87%)	140(40.58%)	
Obese (≥30 kg/m^2)	7(13.46%)	15(4.79%)	26(8.52%)	157(45.51%)	
BMI at age 20					
Normal (<25 kg/m^2)	15(28.85%)	231(73.80%)	233(76.39%)	249(72.17%)	<0.001
Overweight (25-29.9 kg/m^2)	26(50.00%)	70(22.36%)	63(20.66%)	75(21.74%)	
Obese (≥30 kg/m^2)	11(21.15%)	12(3.83%)	9(2.95%)	21(6.09%)	
Physical activity ‡					
Intensive	21(40.38%)	99(32.57%)	88(29.24%)	72(21.30%)	<0.001
Medium	20(38.46%)	100(32.89%)	96(31.89%)	102(30.18%)	
Low	11(21.15%)	105(34.54%)	117(38.87%)	164(48.52%)	
Hypertension					
No	30(57.69%)	191(61.02%)	154(50.49%)	191(55.36%)	<0.001
Yes	22(42.31%)	122(38.98%)	151(49.51%)	154(44.64%)	

*Smoking status: Never smoker, individuals who had never smoked or had smoked <100 cigarettes in their life time; Former smoker, individuals who had smoked at least 100 cigarettes in their lifetime but had quit more than 12 months before recruitment; Current smokers, individuals who are currently smoking or had quit less than 12 months before recruitment.

†Usual BMI refers to BMI at 3yrs before the diagnosis or recruitment.

‡ Intensive: MET≥45/wk.; Medium: MET 27-44.9/wk.; Low: MET<27/wk.

Supplementary Table 4. Selected SNPs, locations, and gene names

SNP name	Linked SNP*	Minor Allele	chromosome	Gene
rs2498804		A	14	AKT1
rs2494738		A	14	AKT1
rs12460555	rs4479364	A	19	AKT2
rs892119		A	19	AKT2
rs3730050		A	19	AKT2
rs4322213	rs4614244	G	1	AKT3
rs1417121	rs1058304	A	1	AKT3
rs3006936	rs1538773	C	1	AKT3
rs10927076	rs4132509	A	1	AKT3
rs10927035	rs2345994	A	1	AKT3
rs12047209	rs12031994	G	1	AKT3
rs1121276		G	1	AKT3
rs9428576		G	1	AKT3
rs3766673		G	1	AKT3
rs4430311		G	1	AKT3
rs7523742		A	1	AKT3
rs12053536	rs7587551	G	2	IRS1
rs16822642	rs1560251	A	2	IRS1
rs17208470		A	2	IRS1
rs6725330		G	2	IRS1
rs1865434	rs11843936	G	13	IRS2
rs1414318	rs7986346	C	13	IRS2
rs1044364	rs12584136	A	13	IRS2
rs7999797		G	13	IRS2
rs9521509		G	13	IRS2
rs4773094		A	13	IRS2
rs4773092		A	13	IRS2
rs7987651		A	13	IRS2
rs9515120		A	13	IRS2
rs4773088		A	13	IRS2
rs9515119		C	13	IRS2
rs4771644		A	13	IRS2
rs7981705		A	13	IRS2
rs4771647		C	13	IRS2
rs11121696	rs1417131	G	1	MTOR
rs1770345		C	1	MTOR
rs4972839	rs3792256	G	2	PDK1
rs1920978		A	2	PDK1
rs12151618		A	2	PDK1
rs13019331		A	2	PDK1

rs6540991	rs6540985	G	1	PIK3CD
rs12568084		A	1	PIK3CD
rs4129341		C	1	PIK3CD
rs4240910		G	1	PIK3CD
rs6541017		G	1	PIK3CD
rs12075554		A	1	PIK3CD
rs11202600	rs11202607	A	10	PTEN
rs926091	rs10788575	A	10	PTEN
rs2248293		G	10	PTEN
rs478839		G	10	PTEN
rs1234221		C	10	PTEN
rs11202596		A	10	PTEN
rs758666	rs2299967	A	7	RHEB
rs6959096	rs12669535	G	7	RHEB
rs13224450		G	7	RHEB
rs717775		C	7	RHEB
rs6951571		A	7	RHEB
rs6972955		A	7	RHEB
rs2058495		A	7	RHEB
rs2299962		A	7	RHEB
rs17635967		G	7	RHEB
rs17713451		A	7	RHEB
rs4549696		A	7	RHEB
rs4710127	rs4710128	A	6	RPS6KA2
rs2984	rs9355578	A	6	RPS6KA2
rs9356531		A	6	RPS6KA2
rs10897487	rs538147	A	11	RPS6KA4
rs7155799	rs17799519	A	14	RPS6KA5
rs8014028	rs11622397	A	14	RPS6KA5
rs180515		G	17	RPS6KB1
rs1051424	rs1292043	G	17	RPS6KB1
rs10274	rs11601325	A	11	RPS6KB2
rs4951662	rs6540776	A	1	RPS6KC1
rs9429904	rs4655415	G	1	RPS6KC1
rs7158047	rs2286914	G	14	RPS6KL1
rs2286913	rs12147862	G	14	RPS6KL1
rs11159109		A	14	RPS6KL1
rs12951596		A	17	RPTOR
rs7208502		A	17	RPTOR
rs6565498		A	17	RPTOR
rs2878052		A	17	RPTOR
rs3751932		G	17	RPTOR
rs4969266		A	17	RPTOR

rs2672890	A	17	RPTOR
rs9915378	A	17	RPTOR
rs7219896	G	17	RPTOR
rs3923514	G	17	RPTOR
rs12937147	G	17	RPTOR
rs9906827	A	17	RPTOR
rs7215564	G	17	RPTOR
rs7219318	A	17	RPTOR
rs2589149	A	17	RPTOR
rs4889863	G	17	RPTOR
rs4889875	A	17	RPTOR
rs2333990	A	17	RPTOR
rs7502124	A	17	RPTOR
rs11651724	A	17	RPTOR
rs7212142	A	17	RPTOR
rs1468033	G	17	RPTOR
rs2048753	A	17	RPTOR
rs7208536	A	17	RPTOR
rs2589150	C	17	RPTOR
rs2280146	G	17	RPTOR
rs7217174	A	17	RPTOR
rs7217223	A	17	RPTOR
rs4969230	G	17	RPTOR
rs2672901	A	17	RPTOR
rs1485330	A	17	RPTOR
rs11150744	C	17	RPTOR
rs7501659	A	17	RPTOR
rs9674559	G	17	RPTOR
rs9901366	A	17	RPTOR
rs7503807	C	17	RPTOR
rs9890502	A	17	RPTOR
rs4969227	A	17	RPTOR
rs1468027	G	17	RPTOR
rs9899051	A	17	RPTOR
rs8071015	C	17	RPTOR
rs12949279	G	17	RPTOR
rs2271608	A	17	RPTOR
rs9897968	A	17	RPTOR
rs4969429	A	17	RPTOR
rs9894401	A	17	RPTOR
rs3829572	G	17	RPTOR
rs4890055	C	17	RPTOR
rs7225525	A	17	RPTOR

rs7209040	A	17	RPTOR
rs9898178	G	17	RPTOR
rs7225574	A	17	RPTOR
rs12948054	A	17	RPTOR
rs7221948	G	17	RPTOR
rs2672893	A	17	RPTOR
rs2589142	A	17	RPTOR
rs2589158	G	17	RPTOR
rs9908270	C	17	RPTOR
rs7224748	A	17	RPTOR
rs9900506	G	17	RPTOR
rs9908195	A	17	RPTOR
rs4889856	G	17	RPTOR
rs2589118	G	17	RPTOR
rs11653499	A	17	RPTOR
rs4889782	G	17	RPTOR
rs901065	A	17	RPTOR
rs9911978	G	17	RPTOR
rs2289762	A	17	RPTOR
rs6420481	G	17	RPTOR
rs8077832	G	17	RPTOR
rs2589143	A	17	RPTOR
rs9901846	A	17	RPTOR
rs3751934	A	17	RPTOR
rs7219745	C	17	RPTOR
rs1062935	G	17	RPTOR
rs12940622	A	17	RPTOR
rs6565484	G	17	RPTOR
rs2271602	A	17	RPTOR
rs12951309	A	17	RPTOR
rs746405	C	17	RPTOR
rs12939076	A	17	RPTOR
rs4969444	A	17	RPTOR
rs12603074	A	17	RPTOR
rs4062178	G	17	RPTOR
rs2672886	G	17	RPTOR
rs6565478	A	17	RPTOR
rs4627412	G	17	RPTOR
rs2589133	G	17	RPTOR
rs999977	A	17	RPTOR
rs2271612	G	17	RPTOR
rs2289766	G	17	RPTOR
rs9911223	A	17	RPTOR

rs12943041		A	17	RPTOR
rs7211818		G	17	RPTOR
rs1877926		A	17	RPTOR
rs4890042		G	17	RPTOR
rs2994329		A	1	SDCCAG8
rs3211995	rs11876	A	16	SLC9A3R2
rs11876		A	16	SLC9A3R2
rs3827665	rs10901219	A	9	TSC1
rs4962225	rs7874234	A	9	TSC1
rs11553763	rs10491535	G	9	TSC1
rs4367688	rs3761840	G	9	TSC1
rs13295430		A	9	TSC1
rs4962081		A	9	TSC1
rs7874234		A	9	TSC1
rs1050700		G	9	TSC1
rs2519757		G	9	TSC1
rs2809243		G	9	TSC1
rs7040593		A	9	TSC1
rs2250057		C	9	TSC1
rs2809246		A	9	TSC1
rs11243929		G	9	TSC1
rs10491534		G	9	TSC1
rs2073636		A	16	TSC2

* Linked SNP: SNPs in high linkage disequilibrium (R2>0.8, distance<500kb) for SNPs not covered by GWAS

Supplementary Table 5. Significant associations between mTOR pathway genetic polymorphisms and RCC risk

Gene	SNP	Alleles (major/minor)	MAF*	Model	OR (95% CI)[‡]	P value	Q Value[§]	P permute[||]	FDR[¶]
AKT3	rs4132509	C/A	0.17	Dominant	1.70(1.26 to 2.30)	5.26E-04			
				Recessive	3.24(1.51 to 6.95)	0.002			
				Additive[†]	1.68(1.30 to 2.17)	6.44E-05	**0.007**	**<0.001**	**0.020**
AKT3	rs3766673	A/G	0.17	Dominant	1.55(1.14 to 2.09)	0.005			
				Recessive	3.26(1.52 to 6.97)	0.002			
				Additive[†]	1.57(1.22 to 2.02)	4.79E-04	**0.014**	**0.001**	**0.096**
AKT3	rs12031994	G/A	0.13	Dominant	1.63(1.19 to 2.23)	0.002			
				Recessive	3.39(1.29 to 8.87)	0.013			
				Additive[†]	1.63(1.23 to 2.15)	5.75E-04	**0.021**	**<0.001**	**0.080**
AKT3	rs4430311	A/G	0.32	Dominant	1.46(1.08 to 1.96)	0.012			
				Recessive	2.00(1.29 to 3.09)	0.002			
				Additive[†]	1.44(1.16 to 1.79)	0.001	**0.022**	**0.001**	**0.083**
AKT3	rs1058304	A/G	0.24	Dominant	1.31(0.98 to 1.75)	0.067			
				Recessive[†]	2.61(1.46 to 4.68)	0.001	**0.026**	**0.001**	**0.097**
				Additive	1.40(1.11 to 1.76)	0.005			
AKT3	rs2345994	G/A	0.32	Dominant	1.46(1.09 to 1.96)	0.011			
				Recessive	1.79(1.15 to 2.77)	0.010			
				Additive[†]	1.41(1.14 to 1.75)	0.002	**0.033**	**0.004**	0.128

* MAF: minor allele frequency.

[†] Indicating best fitting model for each SNP based on smallest p-value

[‡] Adjusted for age, sex, smoking status, BMI at 3 years prior to diagnosis or recruitment, and hypertension;

[§] q value<0.05 was used for significance criteria

||Permutation P value is calculated from 1000 permutations

[¶] FDR: permutation-based false discovery rate

rs4132509 and rs3766673 are in high LD (r^2>0.80)