Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eFigure 1. Diagram of Study Participants and Inclusion Criteria
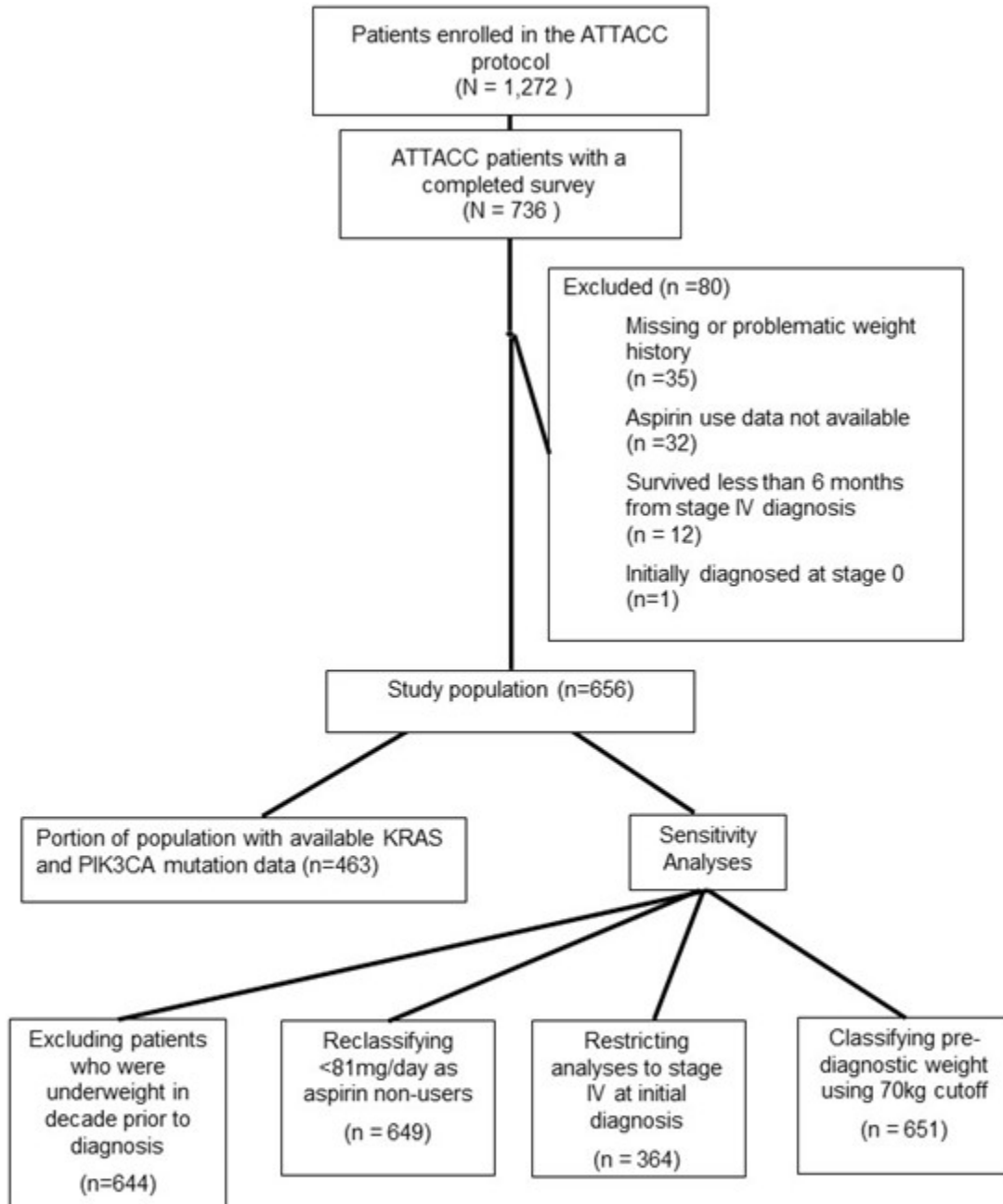
Diagram of study participants and inclusion criteria. A total of 1272 patients enrolled on the ATTACC protocol and 736 completed the survey (57.9%). Out of 736 participants

with a completed survey, 80 (10.9%) were excluded due to missing or problematic weight history, missing aspirin use data, death within 6 months of study entrance or initial diagnosis of stage 0 disease. Of the included study population, 463 (70.6%) had available data on tumor mutations in *KRAS* and *PIK3CA*. Sensitivity analyses were conducted on four subsets of patients: excluding patients who were underweight in the decade prior to diagnosis, reclassifying patients with very low doses of aspirin as non-users, restricting analyses to patients initially diagnosed with stage IV disease and dichotomizing pre-diagnosis weight using a 70kg cutoff.

eFigure 2. Survival from Stage IV Diagnosis Varies Significantly by Pre-diagnosis BMI, But Not Current BMI

A

Pre-diagnosis BMI
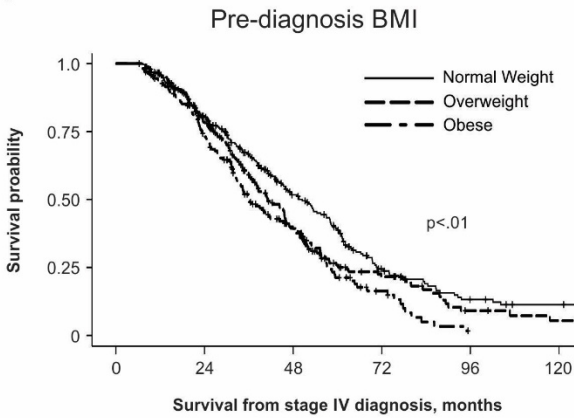
No. at risk

BMI Class						
Normal	251	189	95	33	15	10
Overweight	238	164	66	24	6	3
Obese	167	114	44	11	0	

B
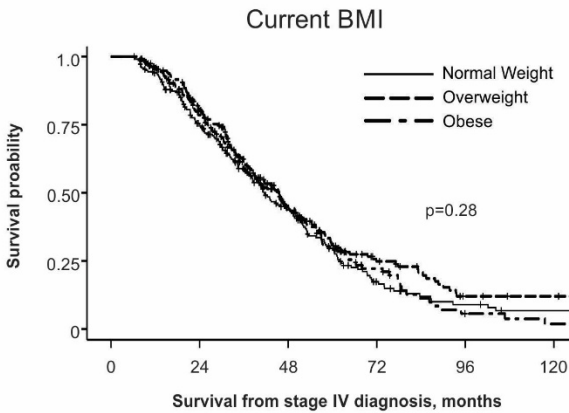
Current BMI

No. at risk

BMI Class						
Normal	217	149	72	21	9	5
Overweight	241	171	72	28	9	7
Obese	196	147	61	19	3	1

Survival from stage IV diagnosis varies significantly by pre-diagnosis BMI, but not current BMI. Kaplan Meier Curve showing survival by normal weight (solid line), overweight (dashed line) or obese (dash dot dash line) pre-diagnosis (A) or current (B) BMI. Number at risk is shown beneath the plot, aligned to the corresponding timepoint.

eFigure 3. Weight Change Acts as a Mediator for the Relationship Between Pre-diagnosis BMI and Survival
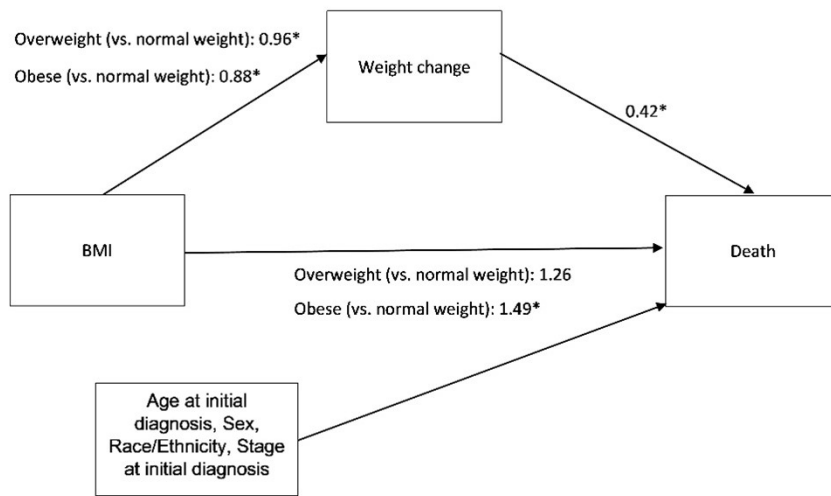
Weight change acts as a mediator for the relationship between pre-diagnosis BMI and survival. Hazard Ratios are presented for direct and indirect effects. *Indicates statistically significant result. Hazard Ratios for co-variates are shown in eTable 2.

eFigure 4. After Adjusting for KRAS and PIK3CA Mutation, Survival From Stage IV Diagnosis Varies Significantly by Pre-diagnosis BMI
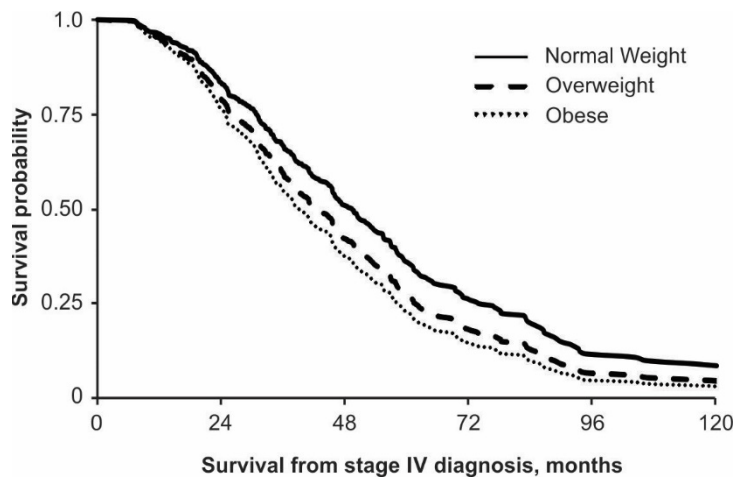
After adjusting for KRAS and PIK3CA mutation, survival from stage IV diagnosis varies significantly by pre-diagnosis BMI. Direct Adjusted survival curves generated from the Cox Proportional Hazards model shown in eTable 4. Pre-diagnosis normal (solid line), overweight (dashed line) or obese (dotted line) are shown.

eFigure 5. Survival From Stage IV Diagnosis by Pre-diagnosis Weight Using 70 kg Cutoff
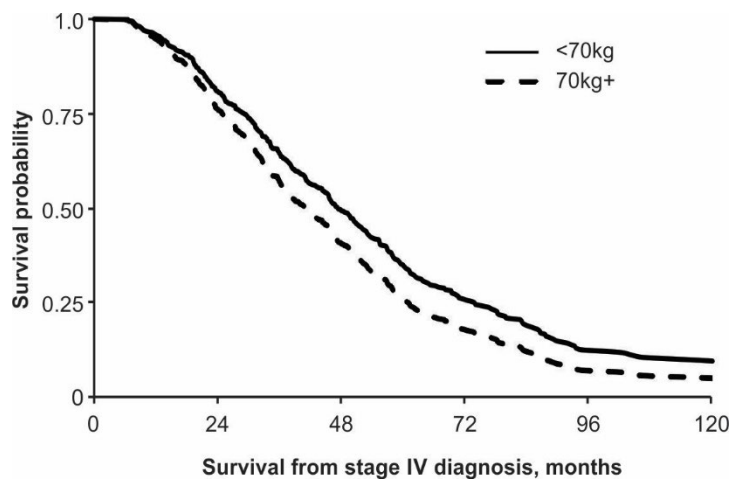
Survival from stage IV diagnosis by pre-diagnosis weight using 70kg cutoff. Direct Adjusted survival curves generated from the Cox Proportional Hazards model shown in eTable 5. Pre-diagnosis weight <70kg (solid line) and 70kg+ (dashed line) are shown.

eFigure 6. Survival From Stage IV Diagnosis by Aspirin Use With Interaction Term Between Aspirin Use and 70 kg Weight
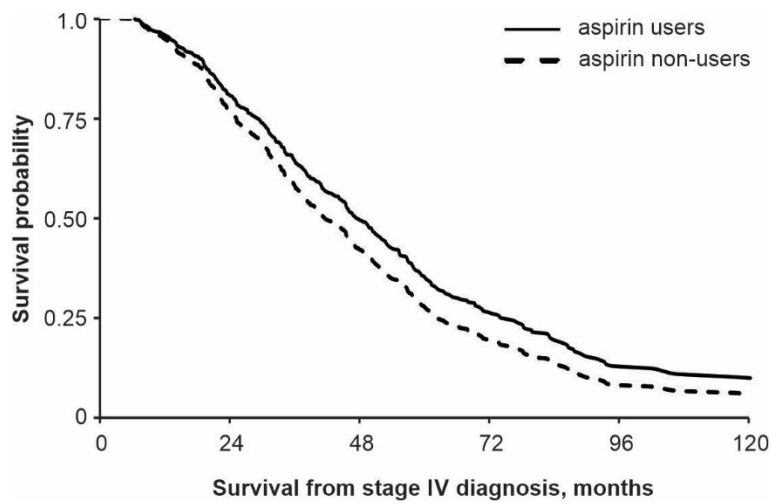
Survival from stage IV diagnosis by aspirin use with interaction term between aspirin use and 70kg weight. Direct Adjusted survival curves are shown among aspirin users (solid line) and non-users (dashed line). Curves were generated from the Cox Proportional Hazards model shown in eTable 6.

eFigure 7. Survival From Stage IV Diagnosis Varies by Pre-diagnosis BMI After Removing Individuals With BMI <18
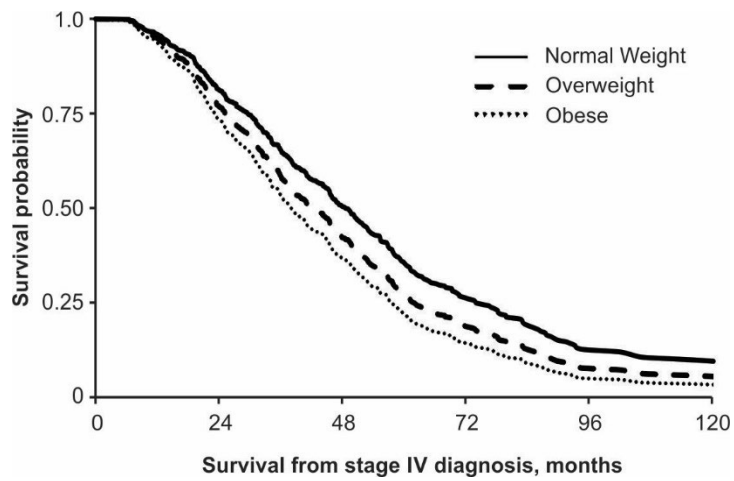
Survival from stage IV diagnosis varies by pre-diagnosis BMI after removing individuals with BMI <18. Pre-diagnosis BMI predicts survival from stage IV diagnosis after removing patients with underweight BMI. Direct adjusted survival curves generated from the Cox Proportional Hazards model shown in eTable 7.

eFigure 8. After Removing Patients With Underweight BMI, Survival Benefit Is Observed With Aspirin Use
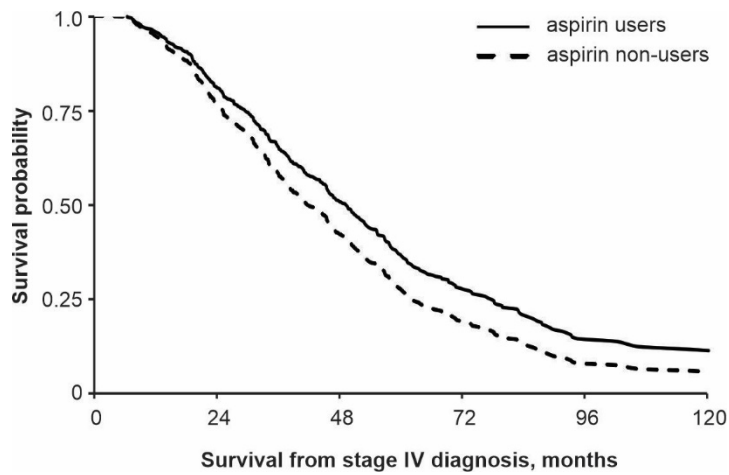
After removing patients with underweight BMI, survival benefit is observed with aspirin use. Survival is compared between aspirin users (solid line) and aspirin non-users (dashed line). Curves were generated from the Cox Proportional Hazards model shown in eTable 8.

eFigure 9. Survival Benefit Was Observed With Postdiagnosis Aspirin Use After Reclassifying Patients With Very Low-dose Aspirin Use as Aspirin Non-users
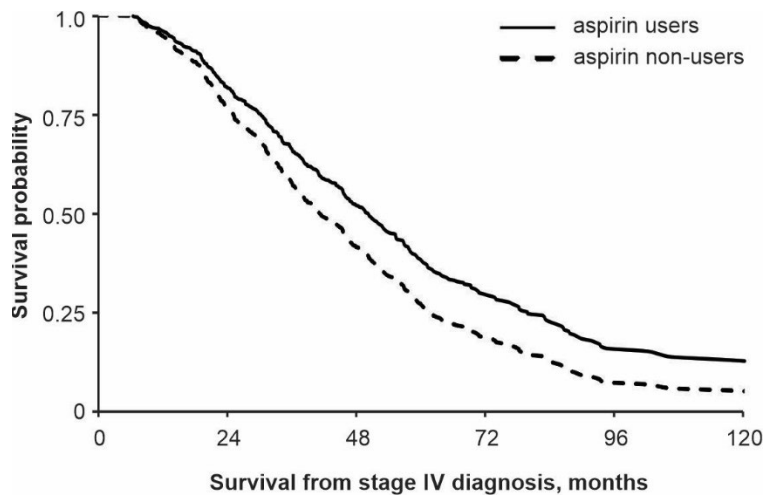
Survival benefit was observed with post-diagnosis aspirin use after reclassifying patients with very low-dose aspirin use as aspirin non-users. Direct Adjusted survival curves generated from the Cox Proportional Hazards model shown in eTable 9. Survival compared between aspirin users (solid line) and aspirin non-users (dashed line).

eFigure 10. Survival by Pre-diagnosis BMI in Patients Initially Diagnosed With Stage IV Disease
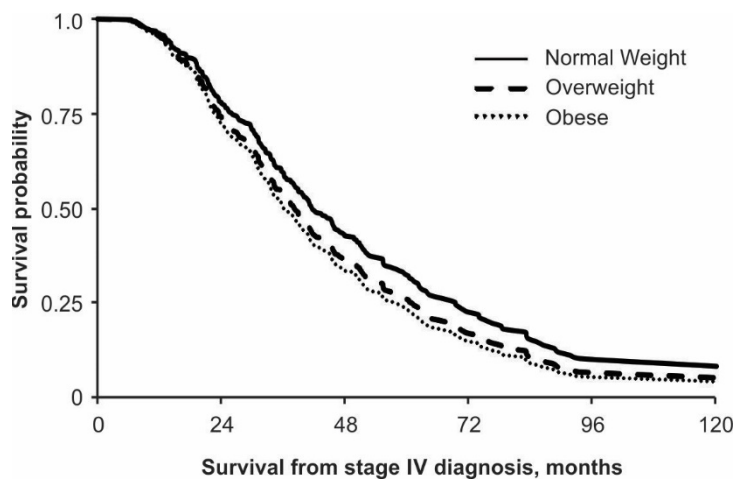
Survival by pre-diagnosis BMI in patients initially diagnosed with stage IV disease. Direct Adjusted survival curves generated from the Cox Proportional Hazards model shown in eTable 10. Pre-diagnosis normal (solid line), overweight (dashed line) or obese (dotted line) are shown.

eFigure 11. Survival Benefit Was Observed With Post-diagnosis Aspirin Use in Patients Initially Diagnosed With Stage IV Disease
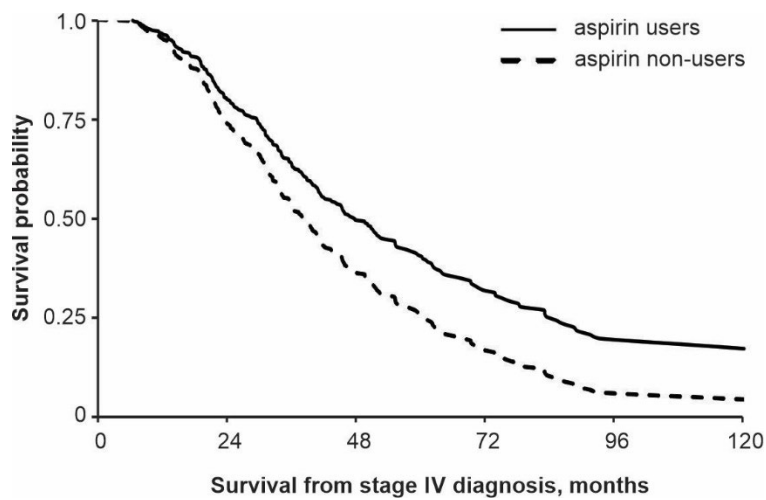
Survival benefit was observed with post-diagnosis aspirin use in patients initially diagnosed with stage IV disease. Direct Adjusted survival curves generated from the Cox Proportional Hazards model shown in eTable 11. Survival compared between aspirin users (solid line) and aspirin non-users (dashed line).

eTable 1. Weight Change and NSAID Dose by Pre-diagnosis BMI Category

eTable 1. Weight change and NSAID use by pre-diagnosis BMI					
	Total	Normal Weight (BMI <25)	Overweight (BMI 25-30)	Obese (BMI 30+)	p value
Weight change[a]	654	250 (38.2)	238 (36.4)	166 (25.4)	<.001
Loss of at least 10%	114 (17.4)	16 (6.4)	38 (16.0)	60 (36.1)	
Within 10% either direction	350 (53.5)	136 (54.4)	130 (54.6)	84 (50.6)	
Gain of at least 10%	190 (29.1)	98 (39.2)	70 (29.4)	22 (13.3)	
NSAID specifics (% total)					
	656				
current aspirin	164 (25.0)	50 (19.9)	62 (26.1)	52 (31.1)	0.03
any aspirin use	188 (28.7)	61 (24.3)	71 (29.8)	56 (33.5)	0.11
	639 [b]				
any non-aspirin	277 (43.4)	109 (44.3)	96 (41.6)	72 (44.4)	0.79
current non-aspirin	260 (40.7)	104 (42.3)	89 (38.5)	67 (41.4)	0.69
Aspirin dose level, n (% of users – any use)[c]	173	54 (31.2)	66 (38.2)	53 (30.6)	0.64
<=81mg/day	120 (69.4)	40 (74.1)	45 (68.2)	35 (66.0)	
> 81mg/day	53 (30.6)	14 (25.9)	21 (31.8)	18 (34.0)	
[a]2 patients had missing data for current weight					
[b]17 patients had missing data for non-aspirin NSAID use					
[c]15 patients reported 'any use' of aspirin, but did not provide dose level or any additional information resulting in fewer case available for dose-level analysis					

eTable 2. Results of Mediation Analysis for Weight Change as a Mediator Between Pre-diagnosis BMI and Survival

eTable 2 Weight change acts as a mediator		
	HR	95% CI
Direct effect of pre-diagnose BMI on a mediator, weight change (ref=normal weight)		
Overweight BMI → Weight change	0.96	0.93, 0.98
Obese BMI → Weight change	0.88	0.86, 0.91
Direct effect of weight change on death	0.42	0.22, 0.81
Direct effect of pre-diagnose BMI on death		
Overweight BMI → death	1.26	0.99, 1.61
Obese BMI → death	1.49	1.15, 1.93
Indirect effect of pre-diagnosis BMI on death through weight change		
Overweight → weight change→ death	1.04	1.00, 1.08
Obese → weight change→ death	1.11	1.02, 1.21
Direct effect of age at initial diagnosis on death (ref=45-65)		
<45 → death	1.13	0.87, 1.46
65+ → death	1.37	1.07, 1.74
Direct effect of sex on death (ref=male)		
Female → death	1.08	0.89, 1.32
Direct effect of race on death (ref= NH Caucasian)		
NH African American and Hispanic → death	0.91	0.71, 1.18
Other → death	0.81	0.53, 1.24
Direct effect of stage at initial diagnosis on death (ref= I/II)		
Stage III	1.27	0.96, 1.68
Stage IV	1.44	1.11, 1.86
NH – Non-Hispanic, Other Race includes Asian/Pacific Islander, American Indian/Alaska Native, and Other, not specified		

eTable 3. Cox Proportional Hazards Model for Survival by Pre-diagnosis BMI Including

eTable 3, Cox proportional Hazards model for survival by pre-diagnosis BMI with continuous weight change variable		
N=649	HR (95% CI)	p value
Pre-Diagnosis BMI		
Normal Weight (<25) (Ref)	1.00	
Overweight (25-30)	1.26 (0.99, 1.60)	0.06
Obese (30+)	1.44 (1.10, 1.88)	0.01
Percent Weight Change (continuous)	0.99 (.099, 1.00)	<.01
Age at initial diagnosis		
<45	1.15 (0.90, 1.48)	0.26
45-65 (Ref)	1.00	
65+	1.36 (1.06, 1.75)	0.02
Sex		
Male (Ref)	1.00	
Female	1.10 (0.90, 1.34)	0.36
Race/Ethnicity		
NH African American and Hispanic	0.93 (0.72, 1.21)	0.60
NH Caucasian (Ref)	1.00	
Other	0.84 (0.57, 1.23)	0.36
Stage at initial diagnosis		
I/II (Ref)	1.00	
III	1.25 (0.91, 1.72)	0.26
IV	1.45 (1.08, 1.94)	0.01
NH – Non-Hispanic, Other Race includes Asian/Pacific Islander, American Indian/Alaska Native, and Other, not specified		

a Continuous Weight Change Variable

eTable 4. Cox Proportional Hazards Model for Survival by Pre-diagnosis BMI Including Select Tumor Mutations, Where Available

eTable 4 Cox Proportional Hazards Model for survival by pre-diagnosis BMI in patients with available mutation data		
N=461	HR (95% CI)	p value
Pre-Diagnosis BMI		
Normal Weight (<25) (Ref)	1.00	
Overweight (25-30)	1.29 (0.98, 1.72)	0.07
Obese (30+)	1.48 (1.07, 2.03)	0.02
Weight Change		
Weight loss (>=10%)	1.09 (0.79, 1.49)	0.61
No Change (Ref)	1.00	
Weight gain (>=10%)	0.74 (0.56, 0.98)	0.04
Age at initial diagnosis		
<45	1.22 (0.90, 1.66)	0.20
45-65 (Ref)	1.00	
65+	1.44 (1.08, 1.92)	0.01
Sex		
Male (Ref)	1.00	
Female	1.04 (0.81, 1.32)	0.78
Race/Ethnicity		
NH African American and Hispanic	0.87 (0.64, 1.18)	0.37
NH Caucasian (Ref)	1.00	
Other	0.76 (0.49, 1.19)	0.23
Stage at initial diagnosis		
I/II (Ref)	1.00	
III	1.24 (0.86, 1.79)	0.24
IV	1.47 (1.06, 2.04)	0.02
KRAS Mutation Status		
WT (Ref)	1.00	
Canonical mutation	1.45 (1.16, 1.82)	0.001
PIK3CA Mutation Status		
WT (Ref)	1.00	
Any Mutation	0.97 (0.75, 1.26)	0.82
NH – Non-Hispanic, Other Race includes Asian/Pacific Islander, American Indian/Alaska Native, and Other, not specified		

eTable 5. Cox Proportional Hazards Model by Pre-diagnosis Weight Using a 70 kg Cutoff for Comparison With Published Results From Prevention Trials

eTable 5, Cox proportional Hazards model for survival by pre-diagnosis weight of 70kg		
N=649	HR (95% CI)	p value
Pre-Diagnosis weight		
<70kg	0.78 (0.61, 1.00)	0.05
70kg+ (Ref)	1.00	
Weight Change		
Weight loss (>=10%)	1.15 (0.89, 1.48)	0.29
No Change (Ref)	1.00	
Weight gain (>=10%)	0.74 (0.59, 0.93)	0.01
Age at initial diagnosis		
<45	1.14 (0.89, 1.47)	0.30
45-65 (Ref)	1.00	
65+	1.38 (1.07, 1.77)	0.01
Sex		
Male (Ref)	1.00	
Female	1.15 (0.91, 1.44)	0.25
Race/Ethnicity		
NH African American and Hispanic	0.95 (0.73, 1.23)	0.70
NH Caucasian (Ref)	1.00	
Other	0.84 (0.57, 1.24)	0.39
Stage at initial diagnosis		
I/II (Ref)	1.00	
III	1.23 (0.90, 1.69)	0.20
IV	1.44 (1.07, 1.93)	0.02
NH – Non-Hispanic, Other Race includes Asian/Pacific Islander, American Indian/Alaska Native, and Other, not specified		

eTable 6. Cox Proportional Hazards Model by Pre-diagnosis Weight Using a 70 kg Cutoff and Post-diagnosis Aspirin Use, Including an Interaction Term

eTable 6 Cox Proportional Hazards Model Including interaction term between pre-diagnosis weight 70kg and post-diagnosis aspirin use		
N=649	HR (95% CI)	p value
Current regular aspirin use*pre-diagnosis 70kg weight		
No Aspirin Use(ref)	1.00	
Aspirin Use <70kg pre-diagnosis	0.84 (0.64, 1.10)	
Aspirin Use ≥70kg pre-diagnosis	0.75 (0.50, 1.12)	
Weight change		
Weight loss (>= 10%)	1.16 (0.89, 1.50)	0.27
No Change (Ref)	1.00	
Weight gain (>=10%)	0.75 (0.60, 0.95)	0.02
Age at initial diagnosis		
<45	1.12 (0.87, 1.44)	0.39
45-65 (Ref)	1.00	
65+	1.39 (1.08, 1.78)	0.01
Sex		
Male (Ref)	1.00	
Female	1.11 (0.88, 1.41)	0.38
Race/Ethnicity		
NH African American or Hispanic	0.94 (0.72, 1.22)	0.63
NH Caucasian (Ref)	1.00	
Other	0.81 (0.55, 1.20)	0.30
Stage at initial diagnosis		
I/II (Ref)	1.00	
III	1.23 (0.90, 1.69)	0.20
IV	1.42 (1.06, 1.91)	0.02
NH – Non-Hispanic, Other Race includes Asian/Pacific Islander, American Indian/Alaska Native, and Other, not specified		

eTable 7. Cox Proportional Hazards Model by Pre-diagnosis BMI, Excluding Underweight (<18 kg/m^2)

eTable 7 Cox Proportional Hazards Model for Survival by Pre-diagnosis BMI, Excluding Underweight Patients		
N=642	HR (95% CI)	p value
Pre-Diagnosis BMI		
Normal Weight (<25) (Ref)	1.00	
Overweight (25-30)	1.27 (1.00, 1.62)	0.05
Obese (30+)	1.47 (1.12, 1.93)	0.006
Weight Change		
Weight loss (>=10%)	1.09 (0.84, 1.42)	0.51
No Change (Ref)	1.00	
Weight gain (>=10%)	0.76 (0.60, 0.95)	0.02
Age at initial diagnosis		
<45	1.16 (0.90, 1.50)	0.26
45-65 (Ref)	1.00	
65+	1.36 (1.06, 1.75)	0.02
Sex		
Male (Ref)	1.00	
Female	1.10 (0.90, 1.35)	0.36
Race/Ethnicity		
NH African American and Hispanic	0.91 (0.70, 1.19)	0.50
NH Caucasian (Ref)	1.00	
Other	0.81 (0.55, 1.20)	0.30
Stage at initial diagnosis		
I/II (Ref)	1.00	
III	1.28 (0.93, 1.77)	0.13
IV	1.48 (1.10, 2.0)	0.009
NH – Non-Hispanic, Other Race includes Asian/Pacific Islander, American Indian/Alaska Native, and Other, not specified		

eTable 8. Cox Proportional Hazards Model by Pre-diagnosis BMI and Post-diagnosis Aspirin Use, Excluding Underweight (<18 kg/m²)

eTable 8 Cox Proportional Hazards Model Including interaction term between pre-diagnosis BMI and post-diagnosis aspirin use, excluding underweight patients (BMI<18)		
N=642	HR (95% CI)	p value
Current regular aspirin use*pre-diagnosis BMI weight		
No Aspirin Use(ref)	1.00	
Aspirin Use Normal BMI (<25)	0.58 (0.38, 0.90)	
Aspirin Use Overweight BMI (25-30)	1.05 (0.74, 1.49)	
Aspirin Use Obese BMI (30+)	0.72 (0.48, 1.08)	
Weight change		
Weight loss (>= 10%)	1.11 (0.86, 1.45)	0.43
No Change (Ref)	1.00	
Weight gain (>=10%)	0.79 (0.63, 1.00)	0.05
Age at initial diagnosis		
<45	1.13 (0.87, 1.46)	0.36
45-65 (Ref)	1.00	
65+	1.38 (1.07, 1.77)	0.01
Sex		
Male (Ref)	1.00	
Female	1.07 (0.87, 1.32)	0.52
Race/Ethnicity		
NH African American or Hispanic	0.89 (0.69, 1.16)	0.41
NH Caucasian (Ref)	1.00	
Other	0.78 (0.52, 1.15)	0.21
Stage at initial diagnosis		
I/II (Ref)	1.00	
III	1.26 (0.92, 1.74)	0.15
IV	1.46 (1.08, 1.96)	0.01
NH – Non-Hispanic, Other Race includes Asian/Pacific Islander, American Indian/Alaska Native, and Other, not specified		

eTable 9. Cox Proportional Hazards Model by Pre-diagnosis BMI and Post-diagnosis Aspirin Use, Reclassifying Users With <81 mg/day as Non-users

eTable 9 Cox Proportional Hazards Model Including interaction term between pre-diagnosis BMI and post-diagnosis aspirin use, reclassifying very low aspirin use as non-use		
N=649	HR (95% CI)	p value
Current regular aspirin use*pre-diagnosis BMI weight		
No Aspirin Use(ref)	1.00	
Aspirin Use Normal BMI (<25)	0.53 (0.34, 0.84)	
Aspirin Use Overweight BMI (25-30)	1.02 (0.71, 1.46)	
Aspirin Use Obese BMI (30+)	0.72 (0.48, 1.08)	
Weight change		
Weight loss (>= 10%)	1.10 (0.85, 1.44)	0.46
No Change (Ref)	1.00	
Weight gain (>=10%)	0.78 (0.62, 0.99)	0.04
Age at initial diagnosis		
<45	1.15 (0.89, 1.48)	0.28
45-65 (Ref)	1.00	
65+	1.36 (1.06, 1.75)	0.02
Sex		
Male (Ref)	1.00	
Female	1.07 (0.87, 1.31)	0.52
Race/Ethnicity		
NH African American or Hispanic	0.89 (0.68, 1.16)	0.38
NH Caucasian (Ref)	1.00	
Other	0.79 (0.54, 1.17)	0.19
Stage at initial diagnosis		
I/II (Ref)	1.00	
III	1.24 (0.90, 1.71)	0.19
IV	1.43 (1.06, 1.92)	0.02
NH – Non-Hispanic, Other Race includes Asian/Pacific Islander, American Indian/Alaska Native, and Other, not specified		

eTable 10. Cox Proportional Hazards Model by Pre-diagnosis BMI, Restricted to Patients Initially Diagnosed With Stage IV Disease

eTable 10 Cox Proportional Hazards Model for Survival by Pre-diagnosis BMI in Patients Initially Diagnosed with Stage IV Disease		
N = 384	HR (95% CI)	p value
Pre-Diagnosis BMI		
Underweight/Normal Weight (<25) (Ref)	1.00	
Overweight (25-30)	1.20 (0.88, 1.65)	0.25
Obese (30+)	1.30 (0.89, 1.89)	0.18
Weight Change		
Weight loss (>=10%)	1.72 (0.82, 1.70)	0.39
No Change (Ref)	1.00	
Weight gain (>=10%)	0.69 (0.51, 0.94)	0.02
Age at initial diagnosis		
<45	1.14 (0.83, 1.56)	0.41
45-65 (Ref)	1.00	
65+	1.06 (0.75, 1.49)	0.74
Sex		
Male (Ref)	1.00	
Female	1.01 (0.77, 1.31)	0.97
Race/Ethnicity		
NH African American and Hispanic	0.99 (0.70, 1.40)	0.95
NH Caucasian (Ref)	1.00	
Other	0.73 (0.44, 1.22)	0.23
NH – Non-Hispanic, Other Race includes Asian/Pacific Islander, American Indian/Alaska Native, and Other, not specified		

eTable 11. Cox Proportional Hazards Model by Pre-diagnosis BMI and Post-diagnosis Aspirin Use, Restricted to Patients Initially Diagnosed With Stage IV Disease

eTable 11 Cox Proportional Hazards Model Including interaction term between pre-diagnosis BMI and post-diagnosis aspirin use, in patients initially diagnosed with stage IV disease		
N=384	HR (95% CI)	p value
Current regular aspirin use*pre-diagnosis BMI weight		
No Aspirin Use(ref)	1.00	
Aspirin Use Normal BMI (<25)	0.30 (0.13, 0.66)	
Aspirin Use Overweight BMI (25-30)	1.11 (0.70, 1.74)	
Aspirin Use Obese BMI (30+)	0.81 (0.46, 1.43)	
Weight change		
Weight loss (>= 10%)	1.21 (0.84, 1.75)	0.31
No Change (Ref)	1.00	
Weight gain (>=10%)	0.78 (0.57, 1.07)	0.12
Age at initial diagnosis		
<45	1.11 (0.81, 1.52)	0.52
45-65 (Ref)	1.00	
65+	1.09 (0.77, 1.53)	0.64
Sex		
Male (Ref)	1.00	
Female	0.96 (0.73, 1.25)	0.76
Race/Ethnicity		
NH African American or Hispanic	0.97 (0.69, 1.37)	0.85
NH Caucasian (Ref)	1.00	
Other	0.67 (0.40, 1.13)	0.14
NH – Non-Hispanic, Other Race includes Asian/Pacific Islander, American Indian/Alaska Native, and Other, not specified		