Supplementary Table 1. Plasma pharmacokinetic parameters for total [^{14}C]-resveratrol equivalents in healthy volunteers that ingested a single dose of either 5 mg or 1 g [^{14}C]-resveratrol.

	Volunteer number	C_{max} (µmol/L)[#]	T_{max} (h)[#]*	AUC (µmol/L/h)	C_{24h} (µmol/L)
5 mg [^{14}C]-resveratrol	**4**	0.7, 0.3	2, 8	6.3	0.12
	12	0.5, 0.2	1, 10	3.8	0.08
	13	0.8, 0.3	0.25, 8	5.1	0.06
	14	0.6, 0.3	1, 8	5.5	0.06
	15	0.7	0.5	4.2	0.10
	16	0.7, 0.5	1, 4	6.5	0.09
	17	0.7, 0.4	1, 6	5.8	0.05
	18	0.5	2	3.0	0.05
	19	0.5, 0.3	1, 6	5.8	0.06
	20	0.7, 0.3	1, 10	6.2	0.12
	Average ± SD	**0.6 ± 0.1**	**1**	**5.2 ± 1.2**	**0.08 ± 0.03**
1.0 g [^{14}C]-resveratrol	**1**	178	1	879	12
	2	135, 44	1, 10	1032	13
	3	107	2	672	17
	5	106	1	779	16
	6	102, 34	1, 10	895	18
	7	91	2	966	12
	8	182, 36	1, 10	1092	14
	9	77, 46	1, 8	800	10
	10	227	0.5	1122	12
	11	165, 56	1, 10	1158	16
	Average ± SD	**137 ± 49**	**1**	**940 ± 162**	**14 ± 2**

[#]Second set of values (for C_{max} and T_{max}) correspond to a second peak in plasma concentration, where detected.
*T_{max} is the time at which the maximum plasma concentration (C_{max}) is detected.

Supplementary Table 2A. Tissue concentrations of [^{14}C]-resveratrol species in patients that received 5 mg resveratrol daily.

Patient ID	Total [^{14}C]-Resveratrol equivalents (pmols/mg tissue)*					Time between [^{14}C]-Resveratrol dose & surgery (hours)	Right or left sided tumour	Pathological tumour stage (Tumour, Node, Metastasis, TNM)
	Mucosa	Muscle	Peritoneal fat	Malignant	Other			
C027	0.19	0.06		0.15		17	Right	T3N0M0
C032	0.05	0.01	0.02	0.04		11.5	Left	TisN0M0
C033	1.03	0.17		0.47		15	Right	T3N0M0
C034	6.19	2.77		6.26	7.17 (polyp)	6	2 tumours: transverse & left colon	T3N0 transverse T3N1 left
C065	0.097	0.084		0.154		16	Left	T4N2M0
C077	0.064	0.086	0.001	0.037		7.5	Right	T3N0M0
C079	6.38	1.208	1.662	7.906		3.5	Right	T2N2M0
C080	0.36	0.237		0.248[#]	Outer ovary 0.219 Inner ovary 0.236	17	Right	N/A Primary ovarian tumour

*pmol/mg tissue is equivalent to µM concentrations, calculated for ease of comparison with plasma and *in vitro* concentrations, by assuming that 1 g tissue is equivalent to 1 mL.

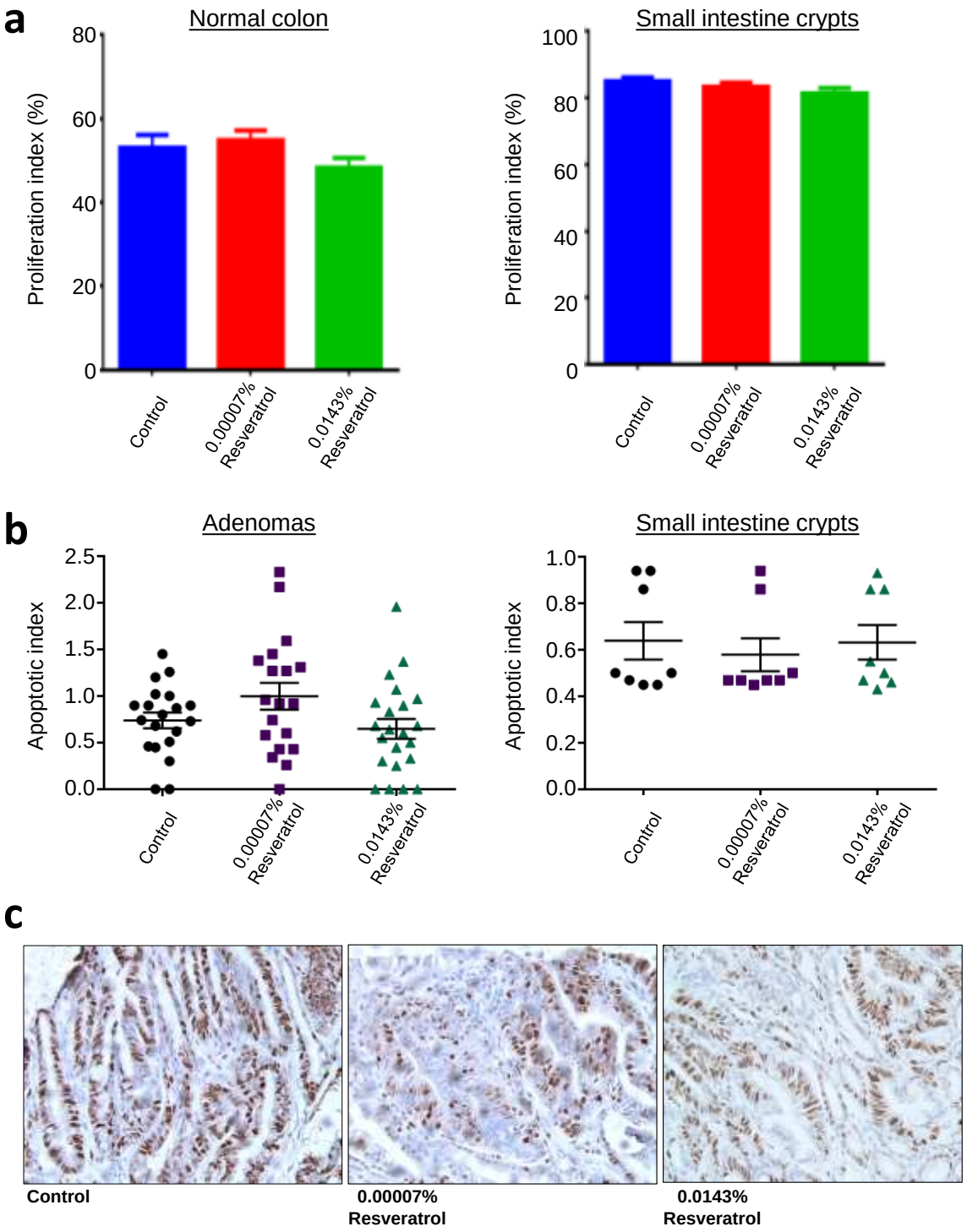
[#]On histological examination the malignant colorectal tissue from this patient was found to be a metastatic ovarian carcinoma. The primary ovarian tumour was also analysed for [^{14}C]-resveratrol content.

Supplementary Table 2B. Tissue concentrations of [^{14}C]-resveratrol species in patients that received 1.0 g resveratrol daily.

Patient ID	Total [^{14}C]-Resveratrol equivalents (pmols/mg tissue)				Time between [^{14}C]-Resveratrol dose & surgery	Right or left sided tumour	Pathological tumour stage (Tumour, Node, Metastasis, TNM)
	Mucosa	Muscle	Peritoneal fat	Malignant			
C040	560.24	717.72		376.07	6	Right	T3N1M0
C043	7.81	8.39		7.61	12	Left	T3N0M0
C048[§]	0.11	<LOD		<LOD	138	Left	T4N1M0
C056[¥]	33.47	2.33	2.13		15	Rectal	T4N1M0
C058	145.86	6.60	6.88	5.17	17.5	Right	T4N1M0
C059	4.46	3.43	0.33	2.84	19.6	Left	T3N1M1
C072	4.68	4.53	0.30	5.17	19.5	Left	T3N1M0
C081	170.10	26.92	11.42	41.26	18.5	Right	T4N2M0

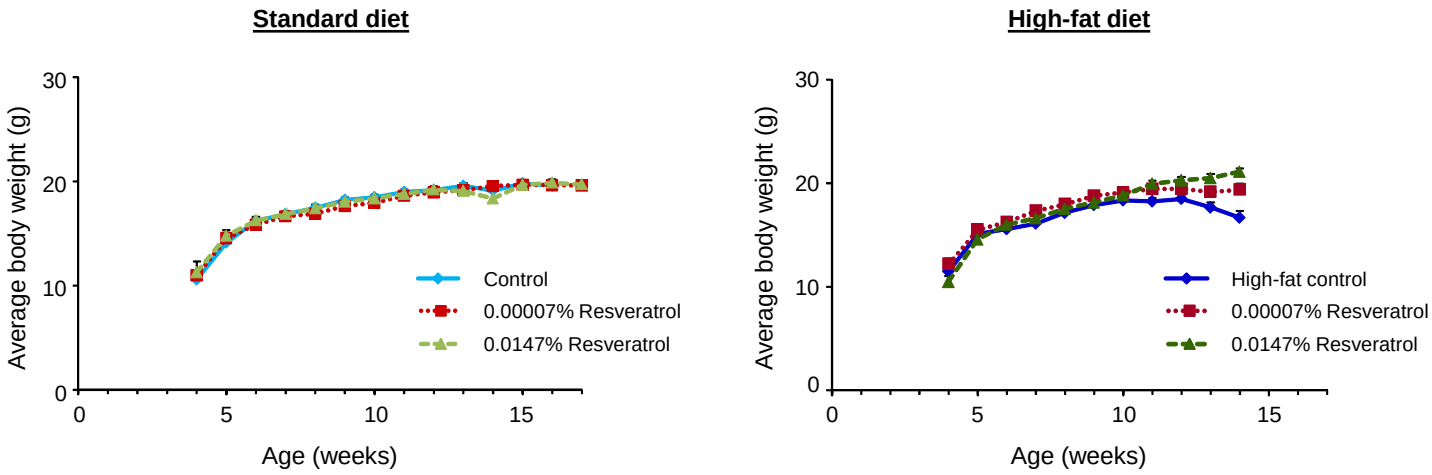
[§]Surgery was delayed, therefore there was a gap of 6 days between the patient taking the [^{14}C]-resveratrol capsule and tissue collection at surgery.

[¥]No malignant tissue available for analysis as it was all required for diagnostic purposes.

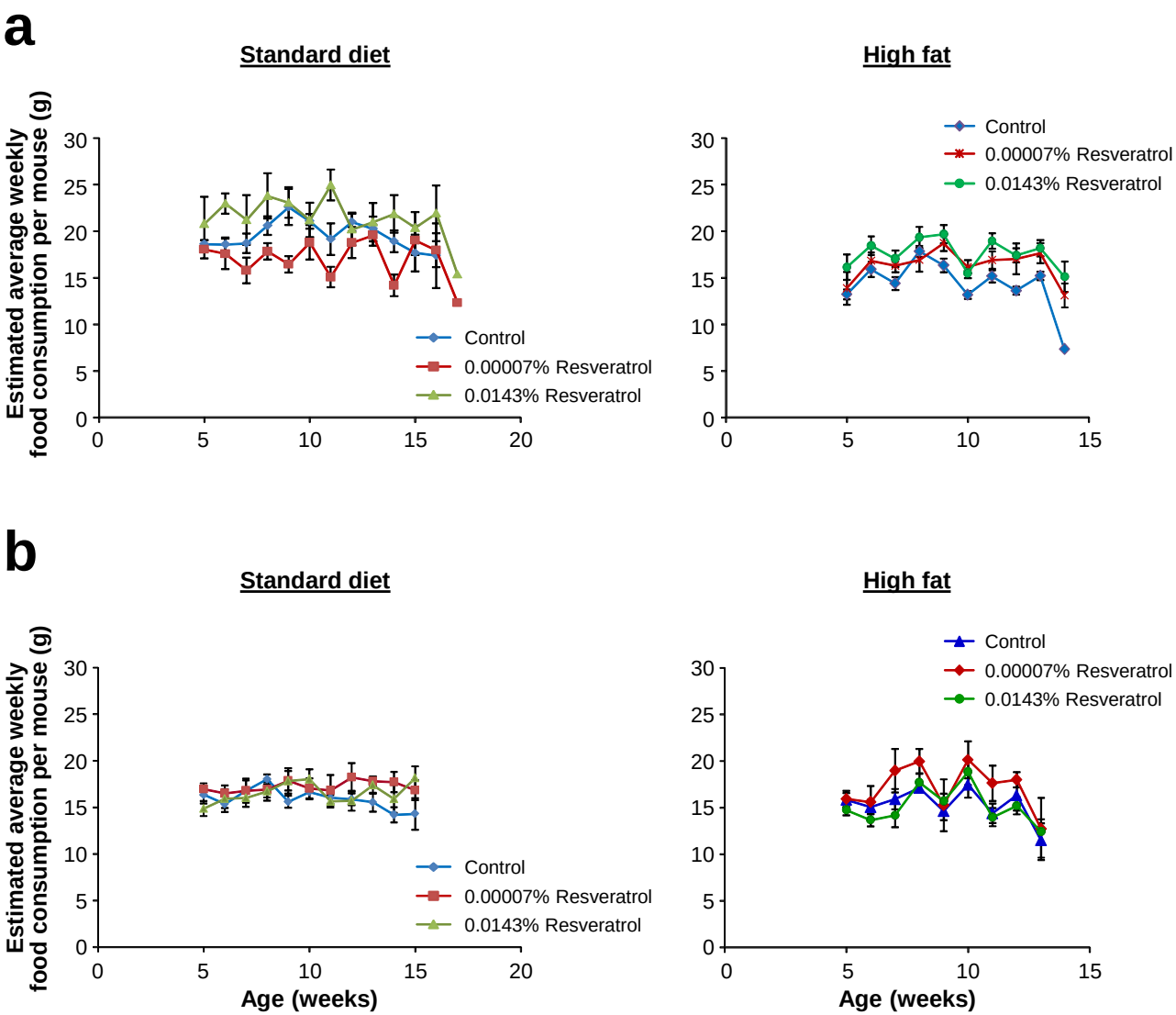


Supplementary Figure 1. Effect of resveratrol on cell proliferation (a & c) and apoptosis (b) in tissues of *Apc*^{Min} mice. Mice were maintained on a high fat diet from weaning (4 weeks of age) supplemented with resveratrol (0.00007 or 0.0143%) and were culled at 14 weeks. (**a**) The extent of proliferation was measured by immunohistochemical staining for nuclear Ki-67 in the crypts of the normal colon and small intestine (n = 6 males and 5 females per group). Values show the percentage (mean ± SEM) of Ki-67 positive cells per field, where 6 different visual fields were scored for each mouse. There was no significant difference in the proliferation index of normal tissue between control mice and those on resveratrol. (**b**) Apoptosis was assessed by immunohistochemical staining for

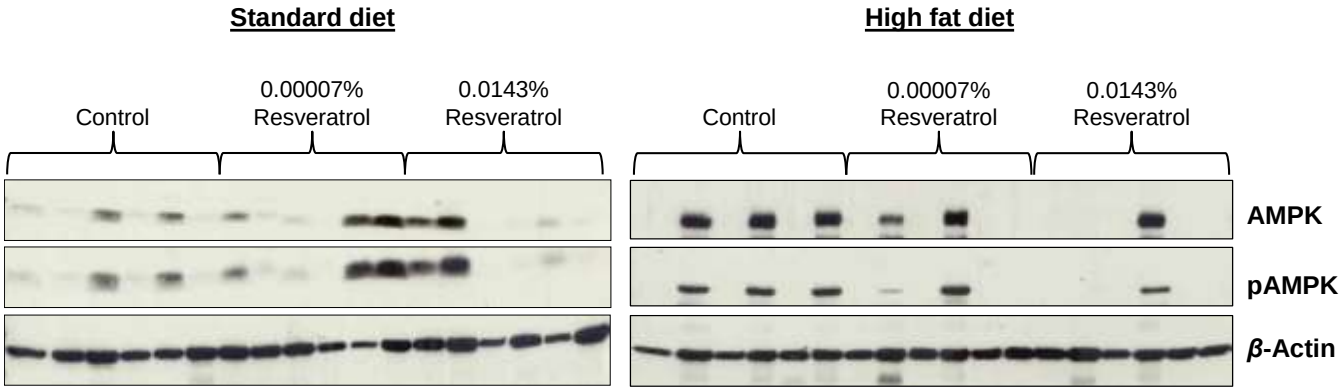
caspase-3 in female mice (4 per group). Positive nuclei were counted in 6 fields of view for adenomas and normal colon whilst 9 fields of view were counted for normal intestinal crypts. There was no evidence that resveratrol, at either dose caused increased apoptosis in these tissues. (**c**) Representative staining for Ki-67 in adenomas of mice on a high-fat diet with and without resveratrol.



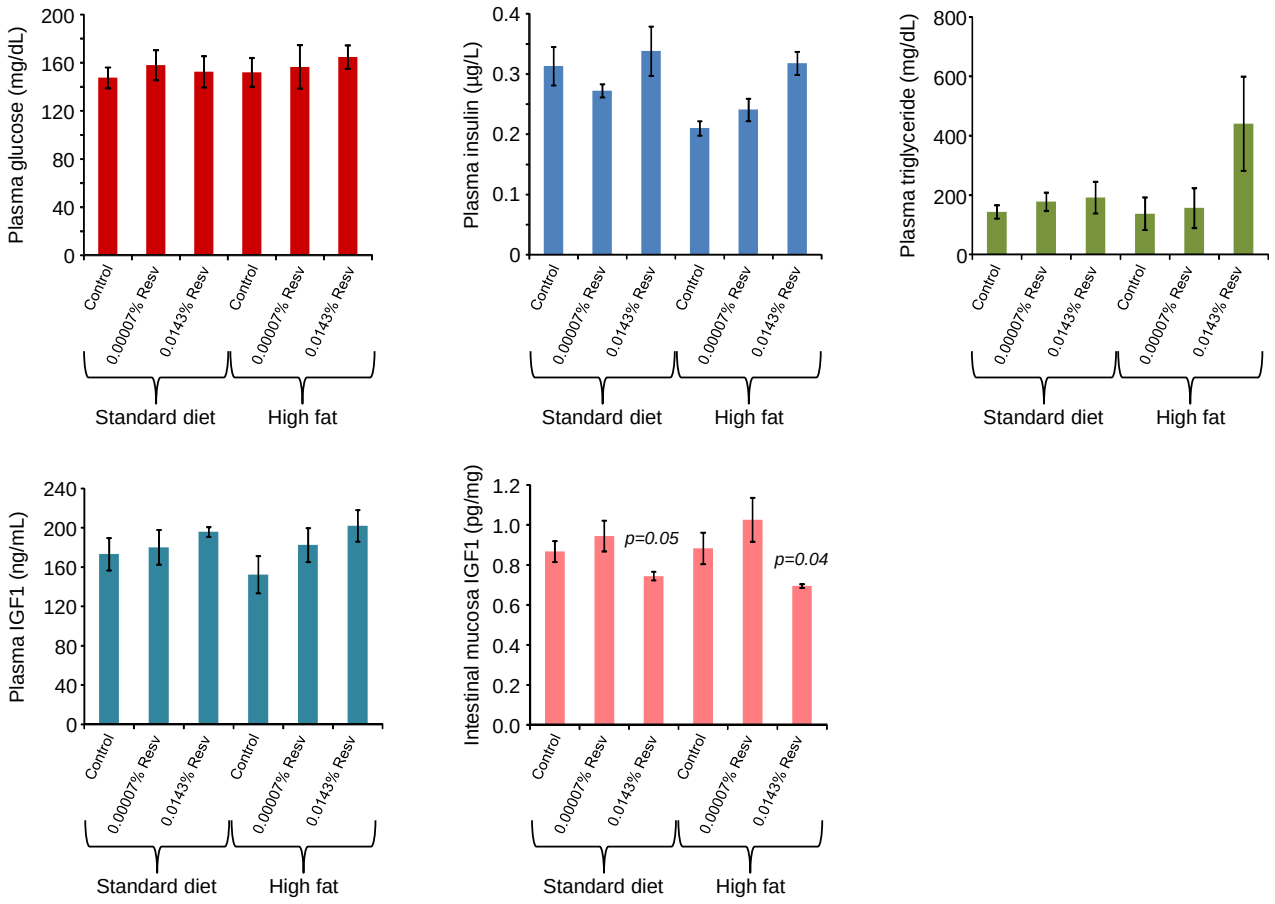
Supplementary Figure 2. Effect of resveratrol and a high-fat diet on body weight of female *Apc*^{Min} mice. Mice were maintained on a standard or high fat diet from weaning (4 weeks of age) supplemented with resveratrol (0.00007 or 0.0143%). Mice on the standard diet were culled at 17 weeks whilst those on the high-fat diet were culled at 14 weeks. The shorter duration was necessary due to the tumour promoting effects of the high-fat diet. Values are the mean + SEM of 14-16 mice per group, except for animals on control high-fat diet at week 14, where *n=8*. Female mice on high fat diet containing low dose resveratrol (0.00007%) had significantly higher body weights than animals on the equivalent control diet (p=0.014); the high dose resveratrol (0.0143%) also increased body weight in high fat diet-fed mice but the difference failed to reach significance (p=0.073). Consumption of a high-fat control diet had no effect on body weight of mice compared to those maintained on the standard diet alone. Resveratrol at either dose had no effect on bodyweight when given with a standard fat diet.



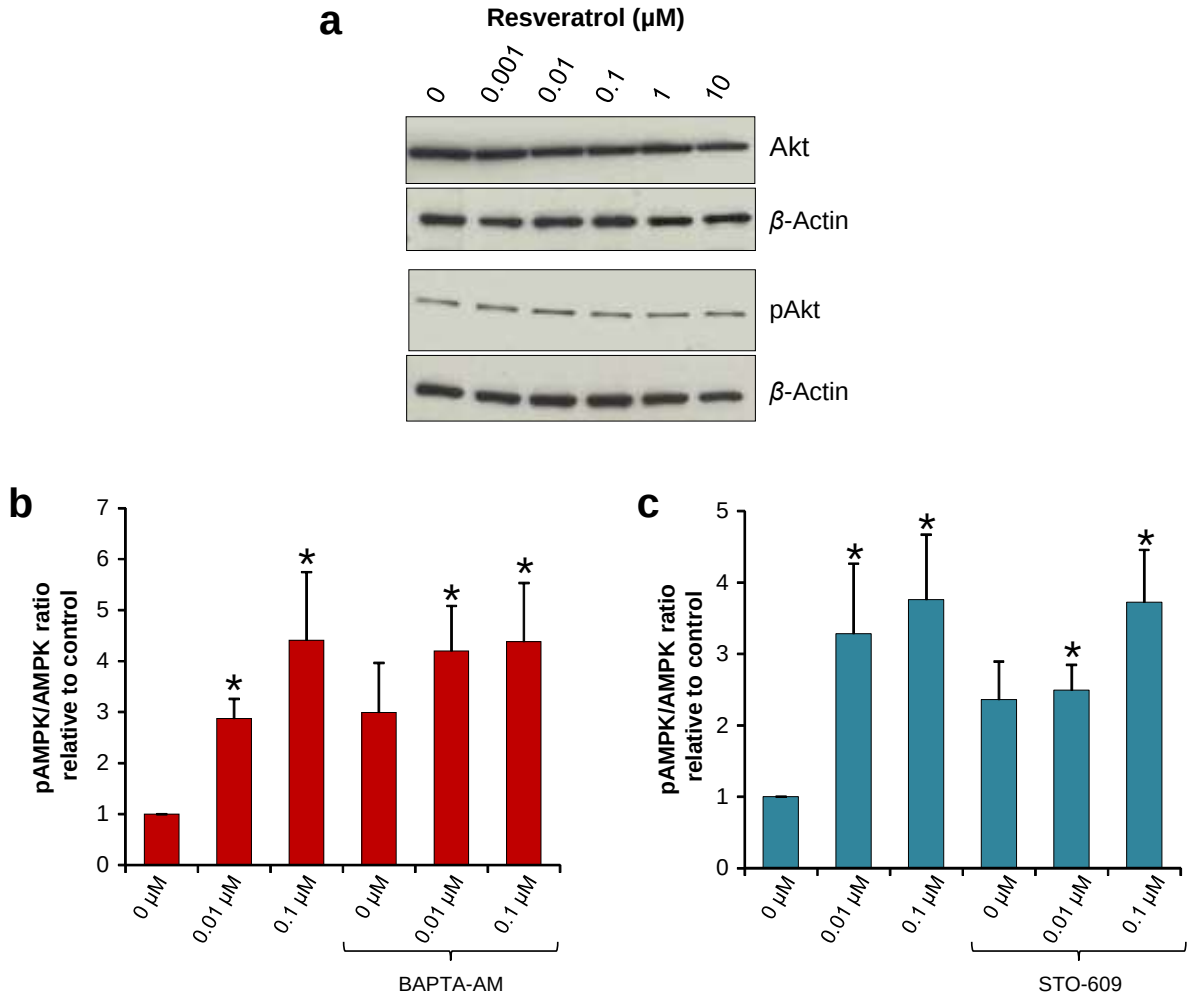
Supplementary Figure 3. Estimated weekly diet consumption by male (a) and female (b) *Apc*^{Min} mice. Mice were maintained on a standard or high fat diet from weaning (4 weeks of age) supplemented with resveratrol (0.00007 or 0.0143%). The average amount of diet consumed per mouse over the course of a week was calculated for each cage, by dividing the amount of food eaten by the number of mice housed, which ranged from 2-4. An estimate of the mass of food (mean ± SEM) consumed by each mouse was then determined by averaging the individual cage value across the number of cages per treatment group (3-9 cages).



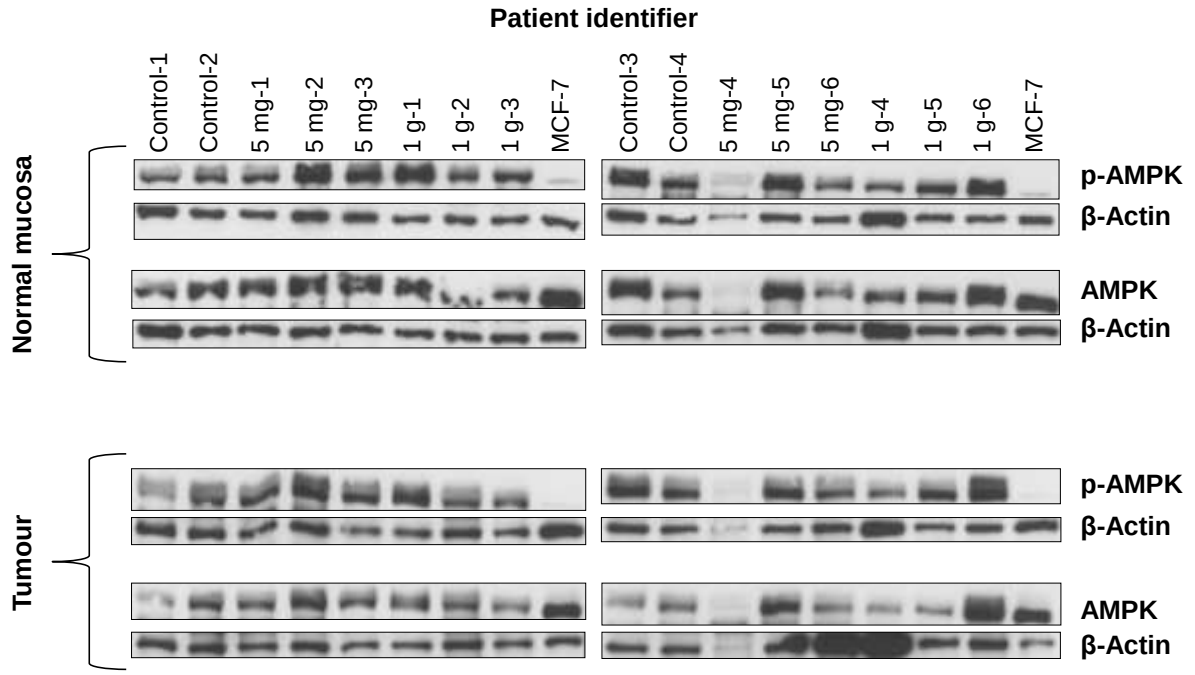
Supplementary Figure 4. Effect of resveratrol on the expression of AMPK in the intestinal mucosa of *Apc*^{Min} mice. Random expression and activation of AMPK within intestinal mucosa of male *Apc*^{Min} mice maintained on a standard or high fat diet from weaning (4 weeks of age) supplemented with resveratrol (0.00007 or 0.0143%). Mice on the standard diet were culled at 17 weeks whilst those on the high-fat diet were culled at 14 weeks. Animals were fasted overnight prior to culling and collection of tissue and plasma. Representative data shown are from 6 mice per group.



Supplementary Figure 5. Effect of resveratrol on metabolic parameters in plasma and intestinal mucosa of fasted male *Apc^{Min}* mice. Mice were maintained on a standard or high fat diet from weaning (4 weeks of age) supplemented with resveratrol (0.00007 or 0.0143%). Mice on the standard diet were culled at 17 weeks whilst those on the high fat diet were culled at 14 weeks; all animals were fasted overnight prior to plasma and tissue collection. Values are the mean ± SEM of 8-11 mice per group for glucose, insulin and triglyceride measurements. Analysis of plasma and mucosal IGF1 levels was conducted on 6 mice per group and the data shown represent the mean ± SEM. There was a large degree of variability between mice and neither resveratrol dose had a significant effect on the concentration of plasma glucose, insulin, triglycerides or IGF1, regardless of the dietary fat content. High dose resveratrol caused a significant reduction in IGF1 levels in the intestinal mucosa of mice on the high fat diet relative to those on the equivalent high fat control diet ($p<0.05$); a similar reduction was observed in mice on the standard diet containing high dose resveratrol but this failed to reach significance ($p=0.05$). The low dose of resveratrol had no effect on tissue IGF1 concentrations.



Supplementary Figure 6. Effects of resveratrol in Apc10.1 mouse adenoma cells. (**a**) Resveratrol treatment of Apc10.1 mouse adenoma cells is not associated with increased expression or phosphorylation of Akt. Cells were treated daily with resveratrol (0.001-10 μM) or DMSO solvent control for 6 days. Four hours after the last addition, cells were harvested and Akt/pAkt levels determined by Western blotting. Representative results are shown. (**b-c**) Cells were pre-exposed for 30 min to BAPTA-AM (20 μM) or STO-609 (5 mg/mL) prior to addition of resveratrol (0.01 or 0.1 μM), then incubated for a further 6 h. Values shown are the mean ± SEM of three independent experiments. Significant differences relative to the solvent only control are shown, where * indicates $p<0.05$. Neither BAPTA-AM or STO-609 had a significant effect on the ability of resveratrol to cause AMPK phosphorylation.



Supplementary Figure 7. Random expression and phosphorylation of AMPK in colorectal surgical tissue obtained from patients participating in the [^{14}C]-resveratrol trial. All patients underwent standard bowel preparation procedures, which includes oral laxatives, and were fasted overnight for varying lengths of time prior to surgery. Both normal mucosa and tumour samples from four untreated control patients, and six each that received 5 mg or 1 g resveratrol daily for the 7 days preceding surgery were analysed by Western blotting; MCF-7 cells were included as a positive control for AMPK expression. There was no evidence of an effect due to resveratrol, however, it should be recognised that confounding factors associated with the surgical procedure, particularly prolonged fasting which is known to activate AMPK, may prevent a true assessment of the ability of resveratrol to modulate AMPK signalling *in vivo*. The sequential numbering system for identifying patients above is arbitrary and does not correlate with the unique patient identifiers shown in Supplementary Tables 2A and B.