Variables	Age interaction			HOMA-IR interaction		
DNA methylation	Case/control F value	Age F value	Case/control*age interaction F value	Case/control F value	HOMA-IR F value	Case/control*HOMA-IR interaction F value
CCL2	0.909	1.769	0.716	2.081	0.592	3.529
IL1β	18.529*	1.225	0.300	6.935*	0.025	0.022
IL6	33.053*	1.228	0.030	18.386*	0.136	0.130
IL10	25.517*	2.024	0.069	5.677*	0.068	0.044
IFNα1	7.125*	0.074	0.454	3.938	0.130	0.000
IFNγ	0.380	0.122	0.035	0.038	0.223	0.092
ΝϜκΒ1	15.287*	1.355	0.190	4.877*	0.123	0.001
ΤΝFα	6.349*	6.565*	1.002	0.989	0.026	2.188
CYP24A1	1.916	1.932	0.052	8.491*	0.472	8.627*
CYP27B1	5.012	1.448	1.300	4.492	0.008	0.656
VDR	2.463	0.889	0.001	0.019	0.024	0.401
RXRa	7.052*	1.988	0.081	1.837	0.812	0.047

## Supplementary Table 5. An ANCOVA model testing whether there is an interaction effect of age and HOMA-IR in DNA methylation

A multivariate regression model using ANCOVA analysis, taking DNA methylation as response variable, CRC as predictor variable and age and HOMA-IR as covariates. There was also taking int account the interaction between predictor variable and covariates. F value is a value on the F distribution, which means variation between means and variation within the samples. Significant interaction is noted as an asterisk (p < 0.05).

Abbreviation: ANCOVA, analysis of covariance, CRC, colorectal cancer, HOMA-IR, homeostatic model assessment of insulin resistance, CCL2, C-C motif chemokine ligand 2, CYP24A1, cytochrome P450 family 24 subfamily A member 1, CYP27B1, cytochrome P450 family 27 subfamily B member 1, IL1 $\beta$ , interleukin 1 beta, IL6, interleukin 6, IL10, interleukin 10, IFN $\alpha$ 1, interferon alpha 1, IFN $\gamma$ , interferon gamma, NF $\kappa$ B1, nuclear factor kappa B 1, TNF $\alpha$ , tumor necrosis factor alpha, RXR $\alpha$ , retinoid X receptor alpha, VDR, vitamin D receptor