The susceptibility to metabolic and proliferative disease

- from genetic predisposition to treatment

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Abstract

Obesity and type 2 diabetes increase the risk of cardiovascular disease. Insulin resistance is highly correlated to type 2 diabetes and both obesity and insulin resistance are risk factors for cancer. Bariatric surgery is an effective strategy to reduce cardiovascular and cancer risk.

In Paper I we tested if bariatric surgery prevents the incidence of cardiovascular events in 607 diabetic participants of the Swedish Obese Subjects (SOS) study. In a long-term follow-up, the incidence of myocardial infarction was lower in subjects who underwent bariatric surgery than in those treated with conventional therapies for obesity. No effect of the surgical treatment was observed on stroke prevention. Paper I shows that bariatric surgery is an effective strategy to prevent myocardial infarction in obese subjects with type 2 diabetes.

In Paper II we aimed to test if carriers of the Insulin receptor substrate 1 (IRS1) rs2943641 T allele, which is associated with lower insulin resistance, have lower cancer incidence. We showed that in morbidly obese subjects from the SOS study cancer incidence was lower in carriers of the *IRS1* T allele than in wild-type homozygotes. The cancer incidence was similar across the *IRS1* genotypes in a population-based cohort study, the Malmö Diet and Cancer (MDC) study. However, cancer incidence was slightly lower in carriers of the *IRS1* T allele than in *IRS1* wild-type homozygotes if only morbidly obese subjects were analysed. A meta-analysis of morbidly obese subjects from those two cohorts confirmed the association of *IRS1* T allele with lower cancer incidence.

Familiar hypercholesterolemia (FH) is a severe form of monogenic hypercholesterolemia associated with increased cardiovascular risk. Both clinical criteria and genetic tests allow performing a diagnosis of FH. Paper III aimed at performing a diagnosis of FH by combining an accurate selection of at-risk individuals through the Dutch Lipid Clinic Network criteria with next-generation sequencing (NGS). We recruited 77 individuals fulfilling clinical criteria for FH. NGS of four genes involved in FH was performed. We detected 26 mutations in 50 subjects (65% success rate). Moreover, we identified a previously unreported splicing-cite mutation that seems to be causative of FH.

Keywords: genetics, insulin resistance, cancer, cardiovascular disease, familiar hypercholesterolemia.

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Genetic diagnosis of familial hypercholesterolemia by targeted next generation sequencing

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