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The IRS1 rs2943641 Variant and Risk of Future Cancer Among Morbidly Obese Individuals

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Context: Obesity and insulin resistance are risk factors for cancer development. The IRS1 rs2943641 genetic variant has been widely associated with insulin resistance.

Objective: The aim of the study was to examine whether the IRS1 rs2943641 associates with cancer incidence in obese individuals.

Design, Setting and Patients: The IRS1 rs2943641 was genotyped in participants from the Swedish Obese Subjects (SOS) study, an intervention trial on the effect of bariatric surgery on mortality and morbidity compared with usual care and in the population-based Malmö Diet and Cancer (MDC) cohort. In both studies, the median follow-up for cancer incidence was about 15 years.

Intervention and Main Outcome Measure: Cancer incidence was assessed in both the SOS and the MDC cohorts through national and local registers.

Results: The IRS1 T allele was associated with lower insulin resistance in both the SOS and the MDC studies. A lower cancer incidence was found in T allele carriers from the SOS control group (hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.62–0.96; \( P = .021 \)) and was restricted to morbidly obese individuals (HR 0.67, 95% CI 0.50–0.91; \( P = .011 \)). No evidence of such association was detected in the surgery group (interaction \( P = .005 \)). In the MDC cohort, a nonsignificant tendency for lower cancer incidence in T allele carriers was observed only in morbidly obese individuals. A meta-analysis of morbidly obese individuals (body mass index \( \geq 40 \text{ kg/m}^2 \)) from the two cohorts strengthened the evidence for the association (HR 0.66, 95% CI 0.50–0.87; \( P = .004 \)).

Conclusions: Our results suggest that the T allele of rs2943641 near IRS1 may associate with lower cancer incidence in morbidly obese individuals. (J Clin Endocrinol Metab 98: E785–E789, 2013)

Obesity is a disease with constantly growing prevalence worldwide (1). The excess in body weight associates with an increase in insulin resistance. Both obesity and insulin resistance increase the risk of developing cancer (2, 3).

Conversely, interventions that reduce body weight and insulin resistance result in a decreased cancer risk (4, 5).

The insulin receptor substrate 1 (IRS1) gene encodes one of the primary mediators of the insulin signaling path-

Abbreviations: BMI, body mass index; CI, confidence interval; HOMA-IR, homeostatic model assessment for insulin resistance; HR, hazard ratio; IRS1, insulin receptor substrate 1; MDC, Malmö Diet and Cancer; SOS, Swedish Obese Subjects.
A genome-wide association study on insulin resistance identified a single-nucleotide polymorphism (rs2943641) in an intergenic region downstream of the IRS1 gene (7) that associates with greater insulin sensitivity. Several studies have confirmed the association between insulin sensitivity and variants near IRS1 and further showed association with metabolic parameters and body fat distribution (8–12).

In this study, we investigate whether IRS1 rs2943641 associates with cancer development among individuals from the Swedish Obese Subjects (SOS) study. In addition, we attempt to replicate findings of the SOS study in the Malmö Diet and Cancer (MDC) cohort.

**Subjects and Methods**

**The SOS study**

The SOS study has been previously described (13). Briefly, the SOS study is a matched, prospective, controlled intervention trial aiming to evaluate the effect of bariatric surgery on mortality and morbidity compared with conventional obesity treatment (for further details, please see Supplemental Materials and Methods, published on The Endocrine Society’s Journals Online web site at http://jcem.endojournals.org). A total of 4047 obese subjects were enrolled in Sweden. Among them, 2010 individuals constituted the bariatric surgery group and a nonrandomized matched control group of 2037 individuals was created based on 18 matching variables. The exclusion criteria included active malignancy during the last 5 years. Individuals with type 2 diabetes at baseline were excluded from the analysis of the current report. DNA was available for 3031 nondiabetic subjects from SOS (version 1.0), and IRS1 rs2943641 was successfully genotyped in 2988 of these subjects.

**The MDC cohort**

The MDC study is a population-based prospective cohort study. All women born from 1923 through 1950 and all men born from 1923 through 1945 living in the city of Malmö, Sweden, were invited to participate. Details on the cohort and the recruitment procedures are described elsewhere (14) (for further details, please see Supplemental Materials and Methods). The present report includes 23,306 individuals, of 28,098 participants, that completed all baseline examinations. Participants whose DNA was not available (n = 1503) or those in whom IRS1 rs2943641 was not successfully genotyped (n = 882) were not included. Individuals with cancer (n = 1594) or diabetes (n = 958) at baseline were also excluded. Data on glucose and insulin levels were available in about 20% of the population of the present report.

**Genotyping of IRS1 rs2943641**

For details on the genotyping of the IRS1 rs2943641 variant, please see Supplemental Materials and Methods. In the SOS study, the success rate was 99%, the minor allele frequency was 38%, and genotypes followed Hardy-Weinberg equilibrium (P = .856, Supplemental Table 1). Genotypes were successfully determined for 97% of the individuals from the MDC cohort, the minor allele frequency was 37%, and the genotypes were in Hardy-Weinberg equilibrium (P = .960, Supplemental Table 1).

**Study endpoints and statistical analyses**

The study endpoints analyzed in the current report were fatal and nonfatal solid cancers. Statistical analyses were carried out using the IBM Statistical Package for Social Sciences version 19.0 (IBM SPSS, Inc, Chicago, Illinois). P values <.05 were considered statistically significant. For further details, please see Supplemental Materials and Methods.

**Results**

**The SOS study cohort**

As expected, baseline homeostatic model assessment for insulin resistance (HOMA-IR) and insulin levels were lower in T allele carriers in the SOS population at baseline (Supplemental Table 2). At the 2- and 10-year follow up, a sustained decrease in body mass index (BMI) was observed in the surgery group, whereas virtually no changes were observed in the control group as previously described (13). Although in the control group, the association between IRS1 T allele and lower HOMA-IR persisted during follow-up, no evidence of association was found in the surgery group during follow-up.

On the cutoff date of the analyses, the median follow-up for cancer incidence was 14.7 years (interquartile range 11.7–17.1 years). A total of 315 cancer events were observed during follow-up. In the SOS control group, IRS1 rs2943641 T allele was associated with a reduced cancer incidence (log-rank P = .019, Figure 1A). In a multivariable Cox proportional hazard model including age, gender, and BMI as covariates, the T allele remained associated with a significantly reduced risk of developing cancer in the SOS control group (hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.62–0.96; P = .021, Table 1). The result was virtually unchanged when smoking or parameters previously associated with near-IRS1 genetic variants were added as covariates in the model (Supplemental Table 3). In a sensitivity analysis after stratifying the SOS control group by the median BMI (40 kg/m^2; range 11.7–17.1 years), a total of 315 cancer events were observed during follow-up. In the SOS control group, IRS1 T allele and lower HOMA-IR persisted during follow-up, whereas virtually no changes were observed in the surgery group, whereas virtually no changes were observed in the control group as previously described (13). Although in the control group, the association between IRS1 T allele and lower HOMA-IR persisted during follow-up, no evidence of association was found in the surgery group during follow-up.

In the surgery group, IRS1 genotypes were not associated with cancer incidence during follow up (log-rank P = .135, Figure 1B; adjusted HR 1.23, 95% CI 0.97–1.57; P = .10, Table 1). An interaction was observed between IRS1 genotypes and the surgical treatment in determining cancer incidence (P = .005). No interaction between gen-
der and IRS1 rs2943641 was observed for cancer incidence in either the SOS control or surgery groups \( (P/H_{11005}/1.43, P/H_{11005}/1.13, \text{respectively}) \).

The MDC cohort To replicate our findings in the SOS study, we next examined the association of IRS1 rs2943641 with lower insulin resistance and cancer in the MDC cohort. Consistent with the findings in the SOS study, baseline HOMA-IR levels were lower in T allele carriers in the MDC cohort (Supplemental Table 2). On the cutoff date of the analyses, the median follow-up for cancer incidence was 14.5 years (interquartile range 14.2–17.4 years). A total of 4963 cancer events occurred during the follow-up in individuals from the MDC cohort. The IRS1 T allele was not associated with cancer incidence in the overall cohort \( (\text{log-rank } P/H_{11005}/0.65, \text{adjusted HR } 1.00, 95\% \text{ CI } 0.96–1.04; P = .92, \text{Table 1}) \). However, among individuals with BMI above 40 kg/m\(^2\) \( (n = 91) \), T allele carriers showed a nonsignificant tendency for lower cancer incidence \( (\text{log-rank } P = .26; \text{adjusted HR } 0.61, 95\% \text{ CI } 0.29–1.29; P = .20, \text{Table 1}) \). When smoking was added as a covariate in the model, the results remained virtually unchanged. No significant IRS1-BMI strata \( (P = .17) \) or IRS1-gender interactions were observed \( (P = .74 \text{ for BMI } \leq 40 \text{ kg/m}^2, \text{ and } P = .15 \text{ for BMI } > 40 \text{ kg/m}^2) \).

A meta-analysis of the SOS control group and the MDC cohort \( (\text{BMI } \geq 40 \text{ kg/m}^2) \) supported the association between the IRS1 T allele and lower cancer incidence \( (\text{HR } 0.66, 95\% \text{ CI } 0.50–0.87; P = .004, \text{Table 1}) \).

**Discussion** Our results suggest that morbidly obese individuals carrying the IRS1 rs2943641 T allele may have a reduced risk of developing cancer. In line with previous studies, among both SOS and MDC study participants, the IRS1 T allele associated with lower insulin resistance. This association is well established and has been widely replicated in several independent studies \( (7, 8, 10) \).

Insulin resistance is a risk factor for cancer \( (3, 5) \). Obese carriers of the IRS1 T allele showed both lower insulin resistance:}

Table 1. Multivariable Cox Proportional Hazards Models for Cancer Events in Participants From the SOS and the MDC Studies for the IRS1 rs2943641 T Allele\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Cases/Noncases</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOS study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>182/1342</td>
<td>0.77 (0.62–0.96)</td>
<td>.02</td>
</tr>
<tr>
<td>BMI &lt; 40 kg/m(^2)</td>
<td>83/679</td>
<td>0.89 (0.65–1.22)</td>
<td>.47</td>
</tr>
<tr>
<td>BMI &gt; 40 kg/m(^2)</td>
<td>99/663</td>
<td>0.67 (0.50–0.91)</td>
<td>.01</td>
</tr>
<tr>
<td>Surgery group</td>
<td>133/1331</td>
<td>1.23 (0.97–1.57)</td>
<td>.10</td>
</tr>
<tr>
<td><strong>MDC study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>4963/18 343</td>
<td>1.00 (0.96–1.04)</td>
<td>.92</td>
</tr>
<tr>
<td>BMI &lt; 40 kg/m(^2)</td>
<td>4943/18 272</td>
<td>1.00 (0.96–1.04)</td>
<td>.98</td>
</tr>
<tr>
<td>BMI &gt; 40 kg/m(^2)</td>
<td>20/71</td>
<td>0.61 (0.29–1.29)</td>
<td>.20</td>
</tr>
<tr>
<td><strong>SOS control and MDC cohorts (BMI &gt; 40 kg/m(^2))</strong></td>
<td>99 + 20/663 + 71</td>
<td>0.66 (0.50–0.87)</td>
<td>.004</td>
</tr>
</tbody>
</table>

\( ^a \) HRs have been adjusted for age, gender, and BMI.

\( ^b \) Summary HRs and corresponding 95% CIs were estimated by fixed and random-effect meta-analysis (Comprehensive Meta-Analysis software; Biostat, Englewood, New Jersey).
resistance and lower cancer incidence during follow-up in the SOS control group but not in the surgery group in which a sustained weight loss was achieved (13). Recent studies suggest that body weight may modulate the associated effects of certain genetic variants on metabolic traits and also on cancer incidence (15, 16). Moreover, a recent genome-wide association study observed an interaction between BMI and the IRS1 locus in determining insulin levels in nonobese individuals (17). In the SOS study, a role of BMI on cancer incidence in relation with IRS1 genotype is not supported by the gene-BMI strata interaction in the control group; however, the significant interaction between IRS1 and bariatric surgery in the overall cohort suggests that body weight modulates the effect of the IRS1 variant on cancer incidence.

To replicate the findings in the SOS study, we examined the association between the IRS1 variant and cancer incidence in another Swedish cohort, the large population-based MDC study. The MDC was selected as a replication cohort because we could not exclude a priori an association between the IRS1 variant and cancer incidence in the general population. In MDC, no evidence for any protective association between the IRS1 T allele and cancer incidence was found. We hypothesized that this lack of association could be due to the difference in BMI between the SOS and MDC populations. Indeed, when the analysis was restricted to morbidly obese individuals from the MDC cohort, we observed a similar trend for protective association between the T allele and cancer incidence as found in the SOS control group. Although we acknowledge that formal replication was not achieved, the results from our meta-analysis suggest that morbid obesity may be needed to uncover the association between the IRS1 variant and lower cancer incidence. The lack of statistical significance in the analysis for the IRS1 variant and cancer incidence among morbidly obese individuals of the MDC cohort may be explained by a lack of statistical power. The reason for using BMI of 40 kg/m² as a cutoff level in the MDC cohort was based on the World Health Organization definition of class III obesity (morbid obesity) (18).

Regarding possible molecular mechanisms, IRS1 acts as mediator of both the metabolic and mitogenic properties of the insulin receptor and of the IGF receptor (6). Changes in IRS1 expression are known to be involved in diabetes and cancer development (19, 20). Genetic variants near the IRS1 locus have been associated with increased IRS1 protein expression in skeletal muscle and/or adipose tissue (7, 11) and with increased IRS1-associated activity of phosphoinositide-3-kinase (7), which may explain the association with lower insulin resistance and lower fasting insulin levels. Lower insulin levels could result in a reduction of the proliferative stimulus through a reduced activation of the mitogenic ERK1 and -2 (21), thus resulting in a lower cancer incidence. Moreover, a genetic variant in high linkage disequilibrium with rs2943641 was reported associated with an increased body fat percentage but with decreased ratio of visceral to sc fat (11). One may thus speculate that the effect of the variants near IRS1 on increased body fat may counteract the potential beneficial effects on cancer incidence in the general population but not in morbidly obese individuals with extreme amounts of sc fat.

In conclusion, our results suggest that the IRS1 rs2943641 T allele may associate with lower risk of incident cancer in morbidly obese individuals. Additional replications in other cohorts as well as in vivo and in vitro studies are required to provide further understanding on the mechanisms underlying the association between the IRS1 variant and human diseases.

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