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Cristina Maglio, Ulrika Ericson, Maria Antonella Burza, Rosellina Margherita Mancina, Carlo Pirazzi, Johanna Andersson Assarsson, Kajsa Sjöholm, Marco Giorgio Baroni, Per-Arne Svensson, Tiziana Montalcini, Arturo Pujia, Lars Sjöström, Olov Wiklund, Lena M. S. Carlsson, Jan Borén, Marju Orho-Melander, and Stefano Romeo

Department of Molecular and Clinical Medicine and Center for Cardiovascular and Metabolic Research (C.M., M.A.B., R.M.M., C.P., J.A.A., K.S., P.-A.S., L.S., O.W., L.M.S.C., J.B., S.R.), the Sahlgrenska Academy, University of Gothenburg, S-413 45 Gothenburg, Sweden; Diabetes and Cardiovascular Disease (U.E., M.O.-M.), Genetic Epidemiology, Department of Clinical Sciences in Malmö, University of Lund, S-205 02 Malmö, Sweden; Human Nutrition Unit (R.M.M., T.M., S.R., A.P.), Department of Medical and Surgical Sciences, University Magna Graecia, I-88100 Catanzaro, Italy; and Endocrinology and Diabetes (M.G.B.), Department of Medical Sciences, University of Cagliari, I-09042 Cagliari, Italy

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 > 40 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-

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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.

way (6). 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; interquartile range, 37–43 kg/m^2), a significant cancer risk reduction associated with the *IRS1* T allele was found only in those with BMI above the median (log-rank $P = .009$; adjusted HR 0.67, 95% CI 0.50–0.91; $P = .011$; Table 1). No significant IRS1-BMI strata interaction was observed ($P = .16$).

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-

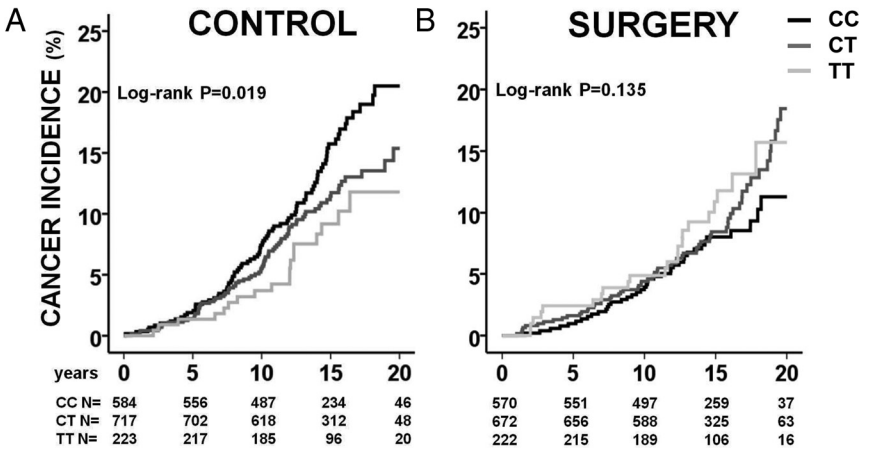

Figure 1. Cumulative incidence of fatal and nonfatal solid cancer in SOS individuals across *IRS1* genotypes separated by control (A) and surgery (B) groups. A, Within the control group, 83 (14%) CC genotype carriers developed cancer (median follow-up, 13.9 [11.3–17.1] years), compared with 80 (11%) heterozygous subjects (median follow-up, 14.3 [11.3–17.1] years) and 19 (9%) TT genotype carriers (median follow up: 14.2 [11.1–16.7]). B, Among the surgery group, 43 (8%) CC genotype carriers developed cancer (median follow up: 14.7 [11.8–17.1] years), compared with 67 (10%) CT heterozygous subjects (median follow up: 14.9 [12.1–17.3] years) and 23 (10%) TT genotype carriers (median follow-up, 14.8 [11.8–16.7] years). Interaction between *IRS1* genotype and treatment (ie, bariatric surgery vs no surgery) on cancer incidence was significant ($P = .005$).

der and *IRS1* rs2943641 was observed for cancer incidence in either the SOS control or surgery groups ($P = .43$ and $P = .13$, 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 (log-rank $P = .65$, adjusted HR 1.00, 95% CI 0.96–1.04; $P = .92$, 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 (log-rank $P = .26$; adjusted HR 0.61, 95% CI 0.29–1.29; $P = .20$, 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 ($P = .74$ for BMI $\leq$ 40 kg/m^2, and $P = .15$ for BMI $>$ 40 kg/m^2).

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

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]

	Cases/Noncases	HR (95% CI)	*P* Value
SOS study			
Control group	182/1342	0.77 (0.62–0.96)	.02
BMI $\leq$ 40 kg/m^2	83/679	0.89 (0.65–1.22)	.47
BMI $>$ 40 kg/m^2	99/663	0.67 (0.50–0.91)	.01
Surgery group	133/1331	1.23 (0.97–1.57)	.10
MDC study			
All	4963/18 343	1.00 (0.96–1.04)	.92
BMI $\leq$ 40 kg/m^2	4943/18 272	1.00 (0.96–1.04)	.98
BMI $>$ 40 kg/m^2	20/71	0.61 (0.29–1.29)	.20
SOS control and MDC cohorts (BMI $>$ 40 kg/m^2)[b]	99 + 20/663 + 71	0.66 (0.50–0.87)	.004

[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/m^2 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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Address all correspondence and requests for reprints to: Stefano Romeo, The Wallenberg Laboratory, Bruna Stråket 16, Sahlgrenska University Hospital, S-413 45 Gothenburg, Sweden. E-mail: stefano.romeo@wlab.gu.se.

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