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## **Abdominal fat and male excess of esophageal adenocarcinoma**

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## **Introduction**

Esophageal and junctional adenocarcinoma (EAC) has a 7-to-1 male predominance.(1) The main risk factors for EAC, obesity and gastroesophageal reflux, are however equally distributed between sexes.(2-4) A predominantly abdominal fat distribution, typical for males, is however a stronger risk factor than BMI,(5-8) and abdominal adiposity might facilitate reflux through increased intra-abdominal pressure. Abdominal adiposity has therefore been suggested to explain the male predominance of EAC. If true, the male-to-female sex ratio in EAC would be low, or absent, among lean patients and high among overweight. We aimed to test this hypothesis.

## Methods

We analyzed data from a population-based nationwide Swedish case-control study, which has been described in detail elsewhere.<sup>(3)</sup> In brief, participants were prospectively included in 1995-1997. Cases were recruited from all 195 Swedish hospital departments involved in these patients. Tumor classification was comprehensive and uniform. Controls were randomly selected and frequency-matched for age and sex of EAC cases. Due to the matching on sex, controls were used to estimate person-years by employing data from the Swedish Register of the Total Population. At personal interviews information on BMI was assessed as: 1) 20 years before interview, 2) 20 years of age, 3) maximum adult BMI, and 4) minimum adult BMI. Incidence rate ratio estimated relative risk (RR). Person-years were calculated by age (<60, 60-69, or 70-79), sex and BMI (<22, 22-<25, or ≥25) derived from the Swedish population. The BMI-distribution in controls was used to estimate person-years in the population. Poisson regression was used to calculate RR and 95% confidence intervals (CI), where log-transformed person-years were included in the model as an offset. To evaluate effect modification of BMI on the association between sex and EAC, we included age, sex, BMI and an interaction term between sex and BMI in the model. Likelihood ratio  $\chi^2$  statistics was used to obtain *P*-value for test of effect modification.

## Results

Included were 451 EAC cases (85% participation) and 820 controls (73%). The male-to-female ratio was 7-to-1. Half of the EAC cases were overweight (BMI  $\geq 25$ ) 20 years before interview. There was no increased RR with increasing levels of BMI in any of the BMI-assessments (Table). Regarding BMI 20 years before interview, the male predominance in overweight participants (RR 5.8, 95%CI 3.9-8.8) was not higher than in lean (RR 7.4, 95%CI 3.9-14.1). The corresponding RRs at age 20 were similar (RR 7.2, 95%CI 3.6-14.3 and RR 7.2, 95%CI 4.8-10.6, respectively). Regarding minimum BMI, there was rather a higher male predominance in lean participants, and for maximum BMI the male predominance was at least as strong in lean (Table).

## Discussion

This study provides no support for the hypothesis that an increased male predominance of EAC correlates with higher BMI.

The population-based design with high participation rates and the possibility to estimate person-years from population-based controls were prerequisites for the study. Recording of all Swedish residents enabled assessment of person-years at risk from which the cases were derived, and thus possible to adjust for age. Other advantages include the thorough tumor classification, personal interviews, and assessment of BMI at different time points. Among weaknesses is possible misclassification of BMI, but any such bias should be similar between cases and controls. Moreover, the low incidence of EAC in women reduced the statistical power.

In conclusion, although abdominal adiposity is clearly overrepresented in men and there is a strong male predominance in EAC, this population-based study with a nearly complete assessment of EAC cases in Sweden found no evidence of an increased age-adjusted male predominance with higher levels of BMI, which argues against abdominal obesity being a key factor in explaining the male predominance.

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**Table.** Age-adjusted relative risk (RR) and 95% confidence interval (CI) of esophageal or gastroesophageal junctional adenocarcinoma in categories of body mass index (BMI) in males compared to females (reference category).

BMI categories	Body mass index			
	20 years before interview	20 years of age	Minimum as adult	Maximum as adult
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
<22	7.4 (3.9-14.1)	7.2 (4.8-10.6)	7.9 (5.4-11.5)	7.5 (1.7-33.8)
22 - <25	5.3 (3.5-8.1)	4.2 (2.7-6.5)	3.6 (2.4-5.5)	8.5 (4.5-15.9)
≥25	5.8 (3.9-8.8)	7.2 (3.6-14.3)	4.2 (1.9-9.3)	5.9 (4.3-7.9)
<i>P</i> -value*	0.68	0.17	0.03	0.55

\* Test of effect modification