Body mass index in early and middle-late adulthood and risk of localised, advanced and fatal prostate cancer: a population-based prospective study

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BACKGROUND: The relationships between body mass index (BMI) during early and middle-late adulthood and incidence of prostate cancer (PCa) by subtype of the disease (localised, advanced) and fatal PCa is unclear.

METHODS: A population-based cohort of 36,959 Swedish men aged 45–79 years was followed up from January 1998 through December 2008 for incidence of PCa (1530 localised and 554 advanced cases were diagnosed) and through December 2007 for PCa mortality (225 fatal cases).

RESULTS: From a competing-risks analysis, incidence of localised PCa was observed to be inversely associated with BMI at baseline (middle-late adulthood; rate ratio (RR) for 35 kg m⁻² when compared with 22 kg m⁻² was 0.69 (95% CI 0.52–0.92)), but not at age 30. For fatal PCa, BMI at baseline was associated with a nonstatistically significant increased risk (RR for every five-unit increase: 1.12 (0.88–1.43)) and BMI at age 30 with a decreased risk (RR for every five-unit increase: 0.72 (0.51–1.01)).

CONCLUSION: Our results indicate an inverse association between obesity during middle-late, but not early adulthood, and localised PCa. They also suggest a dual association between BMI and fatal PCa – a decreased risk among men who were obese during early adulthood and an increased risk among those who were obese during middle-late adulthood.

British Journal of Cancer (2011) 105, 1061 – 1068. doi:10.1038/bjc.2011.319  www.bjcancer.com
Published online 16 August 2011
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Keywords: prostate cancer; body mass index; obesity; body size; prospective cohort study

The aetiology of prostate cancer (PCa), the most common cancer malignancy in men in the developed countries and the second most common one worldwide (Jemal et al, 2011), is still largely unknown (Gronberg, 2003). It seems nonetheless to differ depending on the subtype of the disease at the time of diagnosis, namely localised and advanced PCa cases (Hsing et al, 2007).

Body adiposity is related to both sex hormones and insulin-like growth factor I (IGF-I) (Zumoff, 1988; Pasquali et al, 1991; Yamamoto and Kato, 1993; Kaaks et al, 2000; Lima et al, 2000; Lukanova et al, 2002). Owing to possible relationships between sex hormones and PCa (Platz et al, 2005; Severi et al, 2006) and between IGF-I and PCa (Roddam et al, 2008), body mass index (BMI) has itself been studied as a potential risk factor (Freedland and Platz, 2007). The results, however, are inconsistent.

For incidence of localised PCa, four studies observed a statistically significant inverse relationship with BMI (Gong et al, 2006; Littman et al, 2007; Rodriguez et al, 2007), seven studies observed nonstatistically significant association (Scheurer et al, 2000; MacInnis et al, 2003; Kurahashi et al, 2006; Giovannucci et al, 2007; Pischon et al, 2008; Wallstrom et al, 2009; Stocks et al, 2010) and two studies with a limited number of cases observed a suggestion of direct association, although nonstatistically significant (Cerhan et al, 1997; Putnam et al, 2000).

For incidence of advanced PCa, three studies observed a statistically significant direct association with BMI (Gong et al, 2006; Giovannucci et al, 2007; Rodriguez et al, 2007), six observed no association (Scheurer et al, 2000; Littman et al, 2007; Wright et al, 2007; Pischon et al, 2008; Wallstrom et al, 2009; Stocks et al, 2010), and among four other studies with a small number of cases, two observed a statistically significant direct association (Putnam et al, 2000; MacInnis et al, 2003), but not others (Cerhan et al, 1997; Kurahashi et al, 2006).

To the best of our knowledge, only one study adjusted the multivariable models for BMI during early adulthood when examining the possible relationships between BMI during middle-late adulthood and risk of localised and advanced PCa (Giovannucci et al, 2007).

BMI during middle-late adulthood as well as in earlier stages of life could be critical for the development of PCa (Hsing, 1996; Giovannucci et al, 1997; Gapstur et al, 2002). However, only a limited number of prospective studies examined the relationship between BMI during early adulthood and incidence of PCa by subtype of the disease. Among the studies of localised PCa, inconsistent results were observed with statistically significant inverse (Wright et al, 2007), direct (Scheurer et al, 2000) and null associations (Littman et al, 2007). Four prospective studies examined the association between BMI in early adulthood and...
incidence of advanced PCs, observing null (Schuurman et al, 2000; Litman et al, 2007; Wright et al, 2007) and inverse associations (Giovannucci et al, 1997).

As the available evidence is limited and the results are inconsistent, the aim of our population-based cohort study was to examine the relationships between BMI during early adulthood (age 30 years) and during middle-late adulthood (age 45–79 years) regarding incidence of localised, advanced and fatal PCs.

MATERIALS AND METHODS

The population-based cohort of Swedish men was established during 1997 to 1998, when all eligible men (n = 100 303) aged 45–79 years residing in Västmanland and Örebro counties in central Sweden received an invitation to participate in the study along with a self-administered questionnaire. The questionnaire included questions about current weight, weight at age 30 years, height, educational level, smoking habit, family history of PCa, physical activity and diet. A total of 48 645 men returned the questionnaire.

We excluded participants who returned an incomplete questionnnaire (n = 92), died before 1 January 1998 (n = 55), had a previous cancer diagnosis (n = 2592) or had BMI at baseline age or at age 30 <15, >40 kg m⁻² (n = 196) or missing (n = 8751), thus leaving 36 959 subjects available for the analyses. This population-based cohort is representative of Swedish males aged 45–79 years leaving 36 959 subjects available for the analyses. This population-based cohort of Swedish men was established in terms of age distribution, educational level and prevalence of disease.

The population-based cohort of Swedish men was established in entire Sweden (NBHW, 2000; Orsini et al, 2009) among men aged 65–69 years is 603 in our cohort and 595 in the population-based cohort of Swedish men was established in age 30 years) and during middle-late adulthood (age 45–79 years) regarding incidence of localised, advanced and fatal PCs.

The Cox proportional hazards model was used to estimate PCa incidence rate ratios (RRs) and 95% Wald confidence intervals associated with BMI at baseline age and at age 30 years. Each subject accrued follow-up time from 1 January 1998 until the date of PCa diagnosis, death from any cause or study end (31 December 2008), whichever came first. For fatal PCa analysis, each participant accrued follow-up time from 1 January 1998 until the date of PCa death, death from any cause or study end (31 December 2007), whichever came first.

We categorised BMI at baseline age in six predefined groups (<21, 21–22.9, 23–24.9, 25–27.4, 27.5–29.9 or ≥30 kg m⁻²) to present results in a tabular form. This reference was chosen because in a pooled analysis of 1.46 million white adults, the lowest risk of cancer mortality was observed in the BMI category between 20.0 and 22.5 kg m⁻² (Berrington de Gonzalez et al, 2010).

BMI values at baseline age and at age 30 years were mutually adjusted in both the age-adjusted and multivariable models and were modelled as continuous variables using fractional polynomials (Royston et al, 1999) whenever this provided a better overall fit of the model calculated using the Akaike information criterion (AIC) (Akaike, 1974). All the multivariable analyses were adjusted for baseline age (years), total energy intake (kcal), total physical activity (<37.9, 38–40.9, 41–44.9, ≥45 MET-h per day or missing), years of education (1–9, 9–12 or >12 years), smoking status (current, former or never smoker), family history of PCa (yes, no or don’t know) and personal history of diabetes (yes or no).

We checked whether the proportional hazard assumption was reasonable by means of scaled Schoenfeld’s residuals, which were regressed against the natural logarithm of the survival time. There was no evidence of departure from this assumption.

It is well known that BMI is associated with overall mortality (Berrington de Gonzalez et al, 2010). Therefore, we performed a sensitivity analysis using the competing-risks regression, where all the deaths from other causes than PCs were considered as competing events. This analysis allowed us to evaluate a potential effect of competing risks on the observed results (Fine and Gray, 1999).

All reported P-values were two sided. All statistical analyses were performed with Stata release 11 (StataCorp, College Station, TX, USA).

RESULTS

Age-standardised baseline characteristics by category of BMI at baseline age of the 36 959 study participants are shown in Table 1. Mean age and mean total energy intake did not change significantly across the six levels of BMI at baseline age, as well as prevalence of subjects with family history of PCa. Higher levels of BMI at baseline age were associated with higher values of BMI at age 30 years (Pearson’s correlation coefficient = 0.6). Compared with men in the lowest group of BMI at baseline age, those in the higher groups were more likely to have a personal history of diabetes and less likely to be physically active, well-educated or current smokers.

Mean age at PCa diagnosis for localised and advanced cases was 69 and 74 years, respectively. Mean age at death from PCa was 75 years.

Statistical analysis

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Mean age at PCa diagnosis for localised and advanced cases was 69 and 74 years, respectively. Mean age at death from PCa was 75 years.
Age-adjusted and multivariable RRs for PCa incidence of localised, advanced and fatal PCa in the study population according to BMI levels at baseline age and at age 30 years are presented in Tables 2 and 3, respectively. For localised PCa we observed in the age-adjusted model a left-skewed “inverse U”-shaped relationship with BMI at baseline age. Further adjustment for potential confounders did not substantially change the shape of the relationship. In correspondence with BMI level at baseline age of 35 kg m$^{-2}$, the multivariable model showed a decreased incidence of 29% (6–47%) compared with that at the reference value (22 kg m$^{-2}$). No statistically significant association was observed between BMI at age 30 years and incidence of localised PCa, with a decreased risk of 2% (18–4%) for every 5 kg m$^{-2}$ BMI increase. For every 5 kg m$^{-2}$ BMI at baseline age increase was calculated, as the relationship was modelled in a nonlinear fashion using second-degree fractional polynomials. Multivariable RRs were adjusted for BMI at age 30 years (kg m$^{-2}$), age at baseline (years), total energy intake (kcal), total physical activity (MET-hours per day), smoking status (current, former or never smoker), family history of prostate cancer (yes, no or don’t know) and personal history of diabetes (yes or no).

Abbreviations: CI = confidence interval; RR = rate ratio; BMI = body mass index. *The RRs and 95% CIs were calculated in correspondence with the reference points. **No RR for every 5 kg m$^{-2}$ BMI at baseline age increase was calculated, as the relationship was modelled in a nonlinear fashion using second-degree fractional polynomials. Multivariable RRs were adjusted for BMI at age 30 years (kg m$^{-2}$), age at baseline (years), total energy intake (kcal), total physical activity (MET-hours per day), smoking status (current, former or never smoker), family history of prostate cancer (yes, no or don’t know) and personal history of diabetes (yes or no). The RRs and 95% CIs calculated using competing-risks analysis. All the deaths from other causes than PCa were considered as competing events.
BMI at age 30 years (reference point), kg m$^{-2}$

| BMI increase | For every 5 kg m$^{-2}$ |
|--------------|-------------------------|
| <21 (18)     |                         |
| 21–22.9 (22) |                         |
| 23–24.9 (24) |                         |
| 25–27.4 (26.25) |                   |
| 27.5–29.9 (28.75) |           |
| ≥30 (35)     |                         |

**Localised prostate cancer**

- **Age-adjusted model**
  - No. of cases/person-years: 550/1/20481
  - RR (95% CI): 1.01 (0.92 – 1.12)

- **Multivariable model$^b$**
  - No. of cases/person-years: 153/113
  - RR (95% CI): 1.09 (0.91 – 1.29)

**Advanced prostate cancer**

- **Age-adjusted model**
  - No. of cases/person-years: 12/112
  - RR (95% CI): 1.09 (0.93 – 1.29)

- **Multivariable model$^b$**
  - No. of cases/person-years: 18/108
  - RR (95% CI): 1.11 (0.94 – 1.31)

**Fatal prostate cancer**

- **Age-adjusted model**
  - No. of cases/person-years: 78/113
  - RR (95% CI): 1.31 (1.10 – 1.70)

- **Multivariable model$^b$**
  - No. of cases/person-years: 47/49
  - RR (95% CI): 1.28 (0.99 – 1.67)

**DISCUSSION**

**BMI during middle-late adulthood and incidence of localised, advanced and fatal PCa**

In this population-based prospective cohort study, we observed that high levels of BMI during middle-late adulthood are inversely associated with the incidence of localised PCa. This result is in agreement with some previous prospective studies (Gong et al., 2006; Litman et al., 2007; Rodriguez et al., 2007; Wright et al., 2007), but not all (Cerhan et al., 1997; Putnam et al., 2000; Schuurman et al., 2000; MacLennan et al., 2003; Kurahashi et al., 2006; Giovannucci et al., 2007; Pischon et al., 2008; Wallstrom et al., 2009; Stocks et al., 2010). Among those studies where a statistically significant association was not observed, two suggested an inverse association (Schuurman et al., 2000; Pischon et al., 2008), whereas two studies with a small number of cases suggested a direct association (Cerhan et al., 1997; Putnam et al., 2000).

In contrast to localised PCa, we observed that high BMI levels during middle-late adulthood were associated with a nonsignificant increased risk of advanced PCa. A statistically significant direct association between BMI during middle-late adulthood and incidence of advanced PCa was observed in some previous prospective studies (Putnam et al., 2000; MacLennan et al., 2003; Gong et al., 2006; Giovannucci et al., 2007; Rodriguez et al., 2007), but not all (Cerhan et al., 1997; Schuurman et al., 2000; Kurahashi et al., 2006; Litman et al., 2007; Wright et al., 2007; Pischon et al., 2008; Wallstrom et al., 2009; Stocks et al., 2010).

Our results suggesting an increased risk of fatal PCa are in line with the majority of the previous prospective studies showing a
statistically significant positive association between increased BMI during middle-late adulthood and risk of death from PCa (Calle et al, 2003; Giovannucci et al, 2007; Wright et al, 2007; Stocks et al, 2010), but not all studies (Rodriguez et al, 2001). Similar to the present analysis, in only one previous study the authors adjusted the multivariable analyses also for BMI during early adulthood when examining the relationships between BMI during middle-late adulthood and risk of localised, advanced and fatal PCa (Giovannucci et al, 2007).

BMI during early adulthood and incidence of localised, advanced and fatal PCa

In our study we observed a nonstatistically significant association between BMI during early adulthood (age 30 years) and risk of localised and advanced PCa. Only three prospective studies examined the relationship between BMI during early adulthood and incidence of localised PCa, but they observed inconsistent results: statistically significant direct (Schuurman et al, 2000), inverse (Wright et al, 2007) and null associations (Littman et al, 2007). Four prospective studies examined the association between BMI during early adulthood and incidence of advanced PCa, observing null (Schuurman et al, 2000; Littman et al, 2007; Wright et al, 2007) and inverse associations (Giovannucci et al, 1997).

In our study, a weak evidence of an inverse association between BMI at age 30 years and fatal PCa was observed. Our study is the largest one among the previous prospective studies in terms of the number of cases. The existing evidence from prospective studies about a possible association between early-adult BMI and risk of death from PCa is limited, as only three studies with a small sample size were conducted. However, the results from these studies suggest that a lower BMI at age 30 years may be associated with a lower risk of fatal PCa. Further research is needed to confirm these findings and to explore the mechanisms underlying the association between BMI during early adulthood and the risk of death from PCa.
number of cases are available. Of these, two studies observed a null relationship with fatal PCa (Wright et al, 2007; Burton et al, 2010), whereas one observed a direct association (Okasha et al, 2002), although nonstatistically significant. A dual effect of obesity is suggested by comparing the observed associations between BMI at age 30 years, BMI at baseline age and incidence of fatal PCa: a decreased risk of fatal PCa among men who were obese during early adulthood and an increased risk among those who were obese during middle-late adulthood.

The inconsistent results in studies regarding BMI during late-adulthood and risk of PCa might be because of complex relationships between obesity and hormones, like testosterone and IGF-I. In particular, it is known that obesity is associated with lower serum testosterone concentrations in men (Zumoff, 1988; Pasquili et al, 1991; Lima et al, 2000). Type II diabetes, which is related to obesity, was also observed to be associated with lower levels of testosterone (Giovannucci et al, 1998). Lower testosterone concentrations were in turn observed to be associated with an increased risk of aggressive tumours in two prospective cohort studies (Platz et al, 2005; Severi et al, 2006). Moreover, decreased levels of serum testosterone at PCa diagnosis were also observed to be associated with more aggressive tumours (Hoffman et al, 2000; Schatzl et al, 2001; D’Amico, et al, 2002; Massengill et al, 2003). It has been therefore hypothesised that lower serum testosterone levels may be associated with an increased risk of aggressive tumours and a decreased risk of the nonaggressive ones (Freedland and Platz, 2007; Hsing et al, 2003). Our results are in line with this hypothesis: a higher risk of advanced and fatal PCa and a lower risk of localised PCa among obese men. However, not all studies observed this relationship between aggressiveness of the tumour and serum testosterone levels (Fodstad et al, 2002).

The highest levels of IGF-I were observed in men with a BMI between ~24 and 26 kg m⁻² (Yamamoto and Kato, 1993; Kaaks and Lukanova, 2001; Lukanova et al, 2002). High IGF-I concentrations were observed to be directly associated with PCa incidence (Roddam et al, 2008). This would, at least partly, explain the highest incidence of localised PCa among men within the normal BMI range that we observed in our study and that was also observed among low-grade tumours in the Health Professionals Follow-up Study (Giovannucci et al, 2007). However, other studies observed a linear risk of advanced and fatal PCa and a lower risk of localised PCa among obese men. However, not all studies observed this relationship between aggressiveness of the tumour and serum testosterone levels (Fodstad et al, 2002).

It was suggested that physiologic changes during the years before age 30 may play an important role in the development of PCa (Hsing, 1996; Giovannucci et al, 1997). Obesity during adolescence, which was observed to persist in early adulthood (The et al, 2010), was also observed to be associated with delayed pubertal development (Wang, 2002). As puberty is associated with a steep increase in IGF-I (Keenan et al, 1993; Juul et al, 1994), a delay in puberty could mean a lower cumulative exposure to IGF-I and/or less exposure at crucial ages, and thus a possible reduced risk of PCa among men obese during early adulthood. This is in line with what we observed for advanced and fatal PCa.

The principal limitation of this study is the self-reported, questionnaire-based collection of current weight and weight at age 30 years and height, which are less accurate than anthropometric measures obtained directly by trained professionals. Nonetheless, self-reported current weight and height are shown to be highly correlated with measured weight and height in the Swedish adult population (Kuskowska-Wolk et al, 1989). However, some degree of nondifferential misclassification could have affected the recalled weight at age 30. Our study was observational and therefore we cannot completely exclude the possibility of residual confounding. Nevertheless, age-adjusted and multivariable-adjusted analyses provided overall similar estimates, suggesting that residual confounding is unlikely to explain totally our observed findings. As obesity has been observed to be associated with lower PSA values, and as in obese men the detection of PCa through digital rectal examination may be more complicated (Price et al, 2008), it is possible that some cases of incident PCa might have gone undetected among obese subjects, leading to detection bias. However, there is no national recommendation in Sweden for PSA-based PCa screening and the annual proportion of men aged 55–69 years who underwent a PSA test in the two study counties between 1997 and 2007 is estimated to be between 0% and 7% (Jonsson et al, 2011); thus, any bias introduced by PSA testing should be of limited relevance in our data.

The major strengths of this study include the relatively large size of the cohort, its population-based and prospective design, the relatively large number of incident PCa cases and the completeness of case ascertainment through the Regional and National Cancer Register. These study features substantially reduced the potential risk of selection bias and increased the generalisability of the study findings. As information on exposure was collected prospectively, any nondifferential misclassification would probably weaken rather than exaggerate the true relationship between body size and PCa incidence. Death from other causes than PCa could have impeded the study subjects to develop PCa, especially among obese and underweight men, thus leading to biased estimates. However, we observed only small differences when comparing results from the Cox proportional hazards with the competing-risks models, suggesting that our results were not affected by competing events.

In conclusion, we found some evidence that obesity in middle-aged and elderly men may decrease the risk of localised PCa. On the other hand, our results indicate that there might be a dual effect of obesity on advanced and fatal PCa: an inverse relationship for BMI at age 30 years and a direct relationship for BMI during middle-late adulthood. From a public health perspective, encouraging obesity is not a realistic way to reduce PCa morbidity. The biologic mechanisms behind the relationship between obesity and PCa incidence remain unclear, and thus replication of epidemiological studies and further work in understanding the underlying biologic mechanisms is necessary.

ACKNOWLEDGEMENTS

The work was supported by research grants from the Swedish Cancer Foundation and the Swedish Research Council/Committee for Infrastructure.

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