# Both Low and High Serum IGF-I Levels Associate with Cancer Mortality in Older Men

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**Background:** Although recent population-based studies suggest a U-shaped relationship between serum IGF-I concentration and all-cause mortality, the distribution of death causes underlying this association remains unclear. We hypothesized that high IGF-I levels associate with increased cancer mortality, whereas low IGF-I levels associate with increased cardiovascular disease (CVD) mortality.

**Methods:** Serum IGF-I levels were measured in 2901 elderly men (mean age 75.4, range 69–81 yr) included in the prospective population-based Osteoporotic Fractures in Men Study (Sweden) study. Mortality data were obtained from central registers with no loss of follow-up. The statistical analyses included Cox proportional hazards regressions with or without a spline approach.

**Results:** During the follow-up (mean 6.0 yr), 586 of the participants died (cancer deaths, n = 211; CVD deaths, n = 214). As expected, our data revealed a U-shaped association between serum IGF-I levels and all-cause mortality. Low as well as high serum IGF-I (quintile 1 or 5 *vs.* quintiles 2–4) associated with increased cancer mortality [hazard ratio (HR) = 1.86, 95% confidence interval (CI) = 1.34–2.58; and HR = 1.90, 95% CI = 1.37–2.65, respectively]. Only low serum IGF-I associated with increased CVD mortality (quintile 1 *vs.* quintiles 2–4, HR = 1.48, 95% CI = 1.08–2.04). These associations remained after adjustment for multiple covariates and exclusion of men who died during the first 2 yr of follow-up.

**Conclusions:** Our findings demonstrate that both low and high serum IGF-I levels are risk markers for increased cancer mortality in older men. Moreover, low IGF-I levels associate with increased CVD mortality. **(*J Clin Endocrinol Metab* 97: 4623–4630, 2012)**

Regulated by GH, food intake, and physical activity (1), IGF-I is important for cell growth and proliferation (2) and may reduce inflammation (3). Experimental studies suggest that in addition to regulating postnatal longitudinal growth, IGF-I maintains brain function, cardiovascular performance, and metabolic indices during adulthood (1). Circulating IGF-I, which is mainly liver derived, gradually declines with increasing age (1).

Some clinical studies suggest that high serum IGF-I levels associate with increased risk of cancer (*e.g.* colonic, prostate, and breast cancer) (4–6). GH excess in acromegaly is associated with increased serum IGF-I levels and an increased rate of colorectal cancer (7, 8). A recent relatively small study (cancer deaths, n = 74) reported a significant association between high serum IGF-I levels and increased cancer mortality in elderly men (9).

Increasing clinical evidence suggests that low IGF-I activity is a risk factor for increased cardiovascular disease (CVD) morbidity and mortality. Hypopituitary patients with GH deficiency display increased CVD mortality (10–

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Abbreviations: ApoB, Apolipoprotein B; BMI, body mass index; CRP, C-reactive protein; CV, coefficient of variation; CVD, cardiovascular disease; HR, hazard ratio; MrOS, Osteoporotic Fractures in Men Study.

12). Furthermore, prospective studies have shown an association between low serum IGF-I concentration and increased risk of ischemic heart disease (13) and congestive heart failure (14).

Some (15–19), but not all (20–23), prospective studies suggest that low serum IGF-I levels associate with increased all-cause mortality in the general population. In contrast, few studies suggest that high serum IGF-I levels associate with increased all-cause mortality (17, 24). In three studies, low IGF-I predicted mortality when used in combination with other factors (25–27). In a recent large meta-analysis, the association between circulating IGF-I and all-cause mortality was U-shaped with increased risk of mortality at both low and high serum IGF-I levels (28). However, previous studies have been unable to define the distribution of cause-specific mortality underlying the U-shaped association between serum IGF-I concentration and all-cause mortality.

The present study aimed to analyze the association between serum IGF-I and cause-specific mortality in a large cohort of older men, using state-of-the-art statistical analyses to explore nonlinear associations. We hypothesized that high serum IGF-I levels associate with increased cancer mortality in elderly men, whereas low serum IGF-I levels associate with increased CVD mortality.

## Subjects and Methods

### Study subjects

The multicenter Osteoporotic Fractures in Men Study (MrOS) includes older men in Sweden, Hong Kong, and the United States. The present study involved only the Swedish cohort (n = 3014), which comprises three subcohorts in three different cities: Malmö (n = 1005), Göteborg (n = 1010), and Uppsala (n = 999). In MrOS-Sweden, men aged 69–81 yr were randomly identified using national population registers, contacted, and asked to participate (29). Eligibility for study participation required the ability to walk without aids and the ability to provide self-reported data. There were no other exclusion criteria. Among all subjects contacted, 45% participated in the study.

We investigated whether serum IGF-I concentration at baseline was associated with all-cause, cancer, and CVD mortality and, if so, whether such associations were nonlinear. Measurements of serum IGF-I concentration were available in 2901 of the elderly men (96% of the entire cohort). Blood was drawn during the baseline examination in 2001–2004 and stored at −80 C until assay. Serum samples were collected before 1000 h (68% of the cohort) or around noon (between 1000 and 1500 h, average 1300 h; 32%). Therefore, in additional analyses, time of serum sampling was used as a covariate. The measurements of serum IGF-I concentration were performed in 2005. One subject was excluded from the analyses due to a very high serum IGF-I level (642 ng/ml), which was 5 SD higher than the second highest IGF-I level (398 ng/ml).

### Ethical considerations

We obtained informed consent from all study participants. The MrOS in Sweden was approved by the ethics committees at Göteborg, Lund, and Uppsala Universities.

### Assessment of covariates

Standardized questionnaires (30) were used to gather information about smoking habits and physical activity as well as self-reported medical diagnoses (hypertension, diabetes, cancer, stroke, myocardial infarction, or angina pectoris). This study defined prevalent CVD as a history of stroke, myocardial infarction, and/or angina pectoris. Hypertension was defined as hypertension diagnosis with either self-reported antihypertensive treatment or systolic blood pressure of at least 140 mm Hg (supine blood pressure, measured after 10 min rest). Standard equipment was used to measure height and weight. Body mass index (BMI) was calculated as weight (kilograms)/height $(\text{meters})^2$.

### Assessment of mortality

Mortality data were collected from the population statistics at Statistics Sweden, and follow-up time was recorded as the period between baseline visit (in 2001–2004) and date of death or mortality data collection (December 31, 2009). Cause-of-death data were collected from the Swedish Cause of Death Register, held by the National Board of Health and Welfare in Sweden, which records all deaths in Sweden using International Classification of Diseases (ICD) codes based on the information from death certificates. Data were collected from this register from the start of the study until December 31, 2005, and from evaluation of copies of death certificates from January 1, 2006, until December 31, 2009. Based on the information from the register/death certificate, the underlying death cause was determined for each participant and classified as cancer (ICD-10 codes C00–C97), CVD (I00–I99), or other (noncancer or non-CVD).

### Blood chemistry

Serum was assayed for IGF-I by a double-antibody IGF-binding protein-blocked RIA using a commercial kit (Mediagnost, Tübingen, Germany) with an intraassay coefficient of variation (CV) below 5% and an interassay CV below 8% according to the manufacturer. This assay is reported to quantitatively measure IGF-I in unextracted serum samples. The measurements of serum IGF-I concentration were performed at the local laboratory at Sahlgrenska University Hospital. According to the manufacturer, the median is 161 ng/ml and the 5th and 95th percentiles are 91 and 282 ng/ml, respectively, for men between 60 and 70 yr of age, and the median is 98 ng/ml and the 5th and 95th percentiles are 47 and 207 ng/ml, respectively, for men between 70 and 80 yr of age. In the present study, the median serum IGF-I level was 112 ng/ml and the 5th and 95th percentiles were 57 and 206 ng/ml, respectively. This suggests that our population-based cohort has serum IGF-I levels within the normal range. Finally, according to the manufacturer, the recovery of the IGF-I assay was 100%.

Serum levels of apolipoprotein B (ApoB) and ApoA1 were determined by immunoprecipitation enhanced by polyethylene glycol at 340 nm (Thermo Fisher Scientific, Vantaa, Finland). Highly sensitive C-reactive protein (CRP) was measured using an ultrasensitive method (Orion Diagnostica, Espoo, Finland). The ApoB, ApoA1, and CRP analyses were performed on a Konelab

20 autoanalyzer (Thermo Fisher Scientific). Interassay CV for the Konelab analyses were below 5%.

### Statistical analyses

Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC) and SPSS for Windows version 17.0 (SPSS, Chicago, IL). Unless otherwise stated, the descriptive statistical results at baseline are shown as the mean ± SD. Data that were not normally distributed (serum CRP level and BMI) were logarithmically transformed before the statistical analyses. Furthermore, physical activity (kilometers walked per day) was categorized into quartiles. Differences between quintile groups of serum IGF-I concentration were examined using ANOVA followed by *post hoc* test (Tukey's adjustment for multiple tests) for continuous variables and using $\chi^2$ tests for categorical variables.

We used Cox proportional hazards regression to analyze the association between serum IGF-I concentration (including analyses with serum IGF-I as a quadratic term) and all-cause mortality. Because the quadratic term was statistically significant, the Cox regression analysis used a restricted cubic spline approach for a flexible nonlinear assessment of the hazard ratio (HR) in relation to IGF-I (31). The spline approach was assumed to be less model dependent than corresponding parametric approaches such as polynomials. The positions and the number of knots were selected via Akaike information criterion (32). Five knots at IGF-I percentiles 10, 25, 50, 75, and 90 yielded a small Akaike information criterion value and captured the average curve shape over a systematic assessment of different alternatives. In the analyses using a spline approach, age, MrOS site, and time of serum sampling were used as covariates.

Hazard ratios (quintile 1 or 5 of serum IGF-I concentration compared with quintiles 2–4) were calculated using Cox proportional hazards regression analyses. We adjusted all estimates for age, MrOS site, and time of serum sampling (before 1000 h; yes/no). Moreover, to examine the independent effect of IGF-I on mortality, additional adjustments were made for history of cancer or CVD disease, BMI (log-transformed), quartile of physical activity (kilometers walked per day), current smoking (yes/no), hypertension, diabetes mellitus, serum CRP (log-transformed), and ApoB to ApoA1 ratio. Univariate correlation analyses were performed by calculating Pearson's linear correlation coefficient. A two-sided $P < 0.05$ was considered statistically significant.

## Results

### Baseline characteristics

Table 1 shows the baseline characteristics of the cohort of 2901 elderly men. Higher age associated with lower serum IGF-I concentration. Significant differences between low (quintile 1), intermediate (quintiles 2–4), and high (quintile 5) IGF-I groups were also observed in terms of BMI, serum CRP concentration, and ApoB/ApoA1 ratio. There were no between-group differences in terms of physical activity, current smoking (yes/no), or prevalent diseases (hypertension, diabetes mellitus, history of CVD, and history of cancer) (Table 1). The distribution of men with a history of both CVD and cancer (n = 134) did not differ between groups ($P = 0.22$) (data not shown).

Correlation analysis showed that baseline serum IGF-I concentration correlated weakly and positively with BMI ($r = 0.052$, $P = 0.005$) and ApoB to ApoA1 ratio ($r = 0.045$, $P = 0.02$) and negatively with age ($r = -0.099$, $P < 0.001$) and physical activity ($r = -0.059$, $P = 0.002$).

### U-shaped relation between serum IGF-I and all-cause mortality

During follow-up (mean 6.0, SD 1.5 yr), 586 (20%) of the 2901 participants died. We observed a U-shaped as-

**TABLE 1.** Baseline characteristics of the study population

| Variable | All subjects (n = 2901) | Quintile 1 (n = 579) | Quintiles 2–4 (n = 1740) | Quintile 5 (n = 582) | *P* value |
|---|---|---|---|---|---|
| Serum IGF-I (ng/ml) | 119.4 (47.8) | 63.4 (12.6) | 113.6 (20.8) | 192.4 (37.1) | |
| Age (yr) | 75.4 (3.2) | 76.0 (3.2) | 75.4 (3.2)[a] | 74.9 (3.1)[a,b] | <0.001 |
| BMI (kg/m$^2$) | 26.4 (3.6) | 26.3 (3.7) | 26.3 (3.6) | 26.7 (3.2)[c] | 0.02 |
| CRP (mg/liter) | 4.74 (9.8) | 5.19 (12.6) | 4.36 (7.9) | 5.39 (11.7)[b] | 0.02 |
| ApoA1 (g/liter) | 1.54 (0.30) | 1.54 (0.31) | 1.54 (0.29) | 1.51 (0.29) | 0.09 |
| ApoB (g/liter) | 1.08 (0.25) | 1.06 (0.25) | 1.08 (0.25) | 1.09 (0.25) | 0.06 |
| ApoB/ApoA1 | 0.723 (0.201) | 0.711 (0.212) | 0.721 (0.198) | 0.741 (0.196)[d] | 0.03 |
| Physical activity (km walk/d) | 3.95 (3.15) | 3.96 (3.11) | 4.01 (3.09) | 3.76 (3.35) | 0.07 |
| Current smoking [% (n)] | 8.4 (244) | 7.8 (45) | 8.7 (151) | 8.4 (49) | 0.80 |
| Hypertension [% (n)] | 36.0 (1043) | 34.9 (202) | 35.2 (612) | 39.3 (229) | 0.15 |
| Diabetes mellitus [% (n)] | 9.4 (273) | 10.9 (63) | 8.7 (151) | 10.1 (59) | 0.23 |
| History of CVD [% (n)] | 26.3 (763) | 28.7 (166) | 25.3 (441) | 26.8 (156) | 0.26 |
| History of cancer [% (n)] | 15.7 (455) | 16.2 (94) | 15.3 (266) | 16.3 (95) | 0.75 |

If not otherwise stated, values are given as means (SD). Differences between low IGF-I (range 17–80 ng/ml; quintile 1), intermediate (80–154 ng/ml; quintiles 2–4), and high (154–398 ng/ml; quintile 5) groups of serum IGF-I concentration were examined using an ANOVA followed by Tukey's *post hoc* test for continuous variables and using $\chi^2$ tests for categorical variables.

[a] $P \leq 0.001$ *vs.* quintile 1.

[b] $P < 0.01$ *vs.* quintiles 2–4.

[c] $P < 0.05$ *vs.* quintiles 2–4.

[d] $P < 0.05$ *vs.* quintile 1.

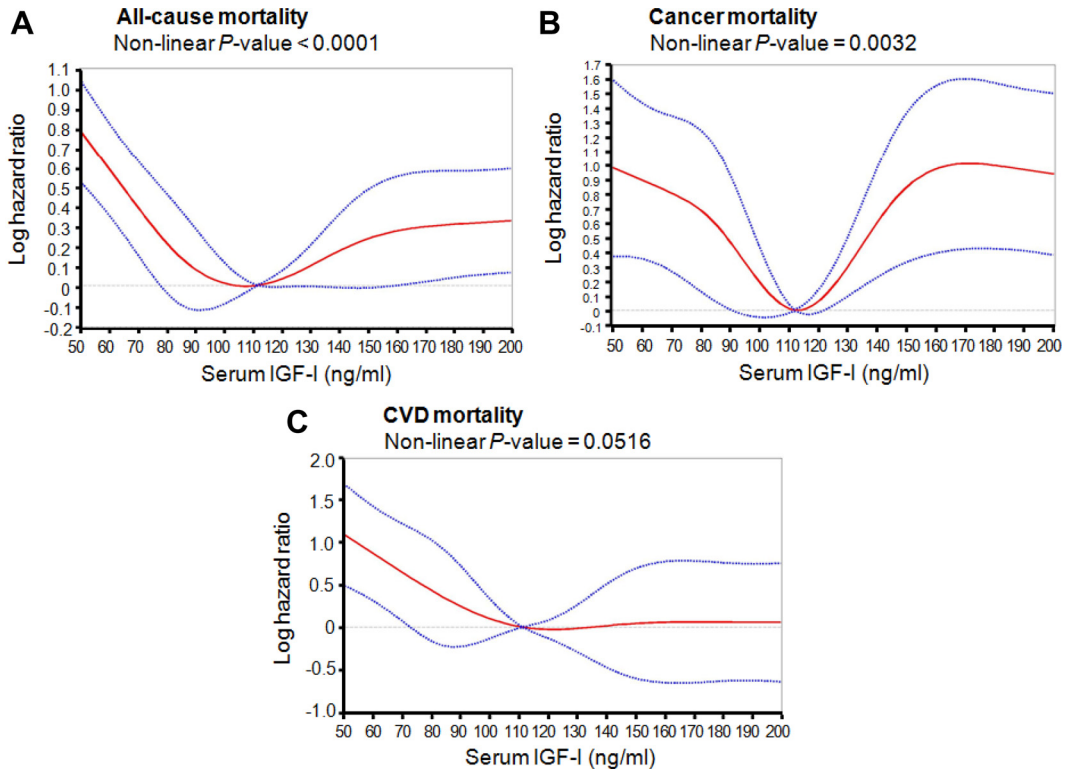


**FIG. 1.** Smoothed plots of HRs for all-cause mortality (A), cancer mortality after exclusion men with a history of cancer before baseline (B), and CVD mortality after exclusion of men with a history of CVD before baseline (C) according to serum IGF-I concentration. HRs (*red solid line*) and 95% CIs (*blue dotted lines*) were estimated by restricted cubic spline Cox regression analysis, using the median serum IGF-I concentration (112 ng/ml) as the reference value. Five knots were positioned at the 10th, 25th, 50th, 75th, and 90th percentiles of serum IGF-I concentration. The *horizontal dashed line* corresponds to the reference (112 ng/ml) HR of 1.0 (no excess mortality rate).

sociation between serum IGF-I concentration and all-cause mortality ($P = 0.002$ for serum IGF-I concentration as a quadratic term). Elderly men with both low and high serum IGF-I concentrations showed a higher all-cause mortality rate compared with those with intermediate values. Using the restricted cubic spline approach, we confirmed a nonlinear association between serum IGF-I concentration and all-cause mortality (Fig. 1A). Furthermore, analysis of risks in the lower and upper quintiles of serum IGF-I concentration *vs.* the intermediate three quintiles (quintiles 2–4) using Cox proportional hazards regression showed that low (HR = 1.67, 95% CI = 1.38–2.03) as well as high (HR = 1.35, 95% CI = 1.10–1.67) serum IGF-I levels associate with increased all-cause mortality.

## Cancer mortality

During the follow-up period, 211 (7.3%) of the elderly men died from a malignant disease. The mean follow-up time in men that died from cancer was 3.7 (SD 1.7) yr compared with 6.2 (1.3) yr in men that did not die from a malignant disease ($P < 0.001$). We tested our hypothesis that high serum IGF-I levels associate with increased cancer mortality. However, restricted cubic spline Cox regression analysis showed that both low and high serum IGF-I concentration associated with increased cancer mortality (nonlinear $P$ value = 0.0003), and this U-shaped association remained after we excluded patients with a history of cancer before baseline (Fig. 1B).

In Cox proportional hazards regression analyses, low as well as high serum IGF-I levels associated with increased cancer mortality (HR = 1.86, 95% CI = 1.34–2.58; and HR = 1.90, 95% CI = 1.37–2.65, respectively) (Table 2). These associations remained after adjustment for multiple covariates and exclusion of men with a history of cancer before baseline (Table 2). Cumulative survival curves illustrated that both men in quintile 1 and men in quintile 5 of serum IGF-I concentration had higher cancer mortality compared with men in quintiles 2–4 (log-rank test $P = 0.001$) (Fig. 2A).

In an attempt to further limit the potential influence of prevalent diseases, we performed analyses that excluded participants with a follow-up time of less than 2 yr (*i.e.* subjects who died within the first 2 yr of follow-up). The significant associations between serum IGF-I levels and cancer mortality remained after this exclusion (Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

## CVD mortality

During the follow-up period, there were 214 CVD deaths (7.4% of the study population). The mean fol-

**TABLE 2.** HRs with 95% CIs of cancer mortality by quintiles of serum IGF-I concentration

| | Quintile 1 (<20th percentile) | Quintiles 2–4 (20–80th percentile) | Quintile 5 (>80th percentile) |
|---|---|---|---|
| Cancer mortality | | | |
| Deaths [n (%)] | 58 (10.0) | 97 (5.6) | 56 (9.6) |
| Base model | 1.86 (1.34–2.58) | 1.0 (referent) | 1.90 (1.37–2.65) |
| Multivariate model A | 1.84 (1.32–2.56) | 1.0 (referent) | 1.83 (1.30–2.56) |
| Multivariate model B | 1.84 (1.32–2.57) | 1.0 (referent) | 1.86 (1.32–2.61) |
| Multivariate model C | 1.85 (1.33–2.58) | 1.0 (referent) | 1.80 (1.22–2.38) |
| Cancer mortality with exclusions[a] | | | |
| Deaths [n (%)] | 36 (7.4) | 65 (4.4) | 39 (8.0) |
| Base model | 1.74 (1.15–2.62) | 1.0 (referent) | 2.01 (1.35–3.00) |
| Multivariate model A | 1.71 (1.13–2.59) | 1.0 (referent) | 1.94 (1.29–2.91) |
| Multivariate model B | 1.71 (1.12–2.59) | 1.0 (referent) | 1.98 (1.32–2.99) |
| Multivariate model C | 1.70 (1.12–2.58) | 1.0 (referent) | 1.92 (1.27–2.89) |

HRs were calculated using Cox proportional hazards regression. In the base model, adjustment was made for age, MrOS site, and time of serum sampling. Multivariate model A was adjusted for age, MrOS site, time of serum sampling, BMI (log-transformed), and quartile of physical activity (kilometers walked per day). Multivariate model B was adjusted for age, MrOS site, time of serum sampling, BMI (log-transformed), quartile of physical activity (kilometers walked per day), current smoking (yes/no), hypertension, and diabetes mellitus. Multivariate model C was adjusted for age, MrOS site, time of serum sampling, BMI (log-transformed), quartile of physical activity (kilometers walked per day), current smoking (yes/no), hypertension, diabetes mellitus, serum CRP (log-transformed), and ApoB to ApoA1 ratio.

[a] Men with a history of cancer at baseline were excluded.

low-up time in men that died from CVD was 3.7 (SD 1.8) yr compared with 6.2 (1.2) yr in men that did not die from CVD ($P < 0.001$). Using the restricted cubic spline approach, we observed a nonlinear relation (nonlinear $P$ value = 0.0094) that lost significance after we excluded men with a history of CVD before baseline (Fig. 1C). Thus, only low serum IGF-I concentration associated with increased CVD mortality (Fig. 1C). Analysis of risks in the lower and upper quintiles of serum IGF-I concentration *vs.* that in the intermediate three quintiles (quintiles 2–4) using Cox proportional hazards regression confirmed that low serum IGF-I levels associated with increased CVD mortality (HR = 1.48, 95% CI = 1.08–2.04) (Table 3). Furthermore, the significant association between low serum IGF-I levels and CVD mortality remained after adjustment for multiple covariates (Table 3) and exclusion of men who died during the first 2 yr of follow-up (Supplemental Table 2). Finally, cumulative survival curves further illustrated that men in the lowest quintile had higher CVD mortality compared with men in quartiles 2–4 (log-rank test $P$ = 0.003) (Fig. 2B).

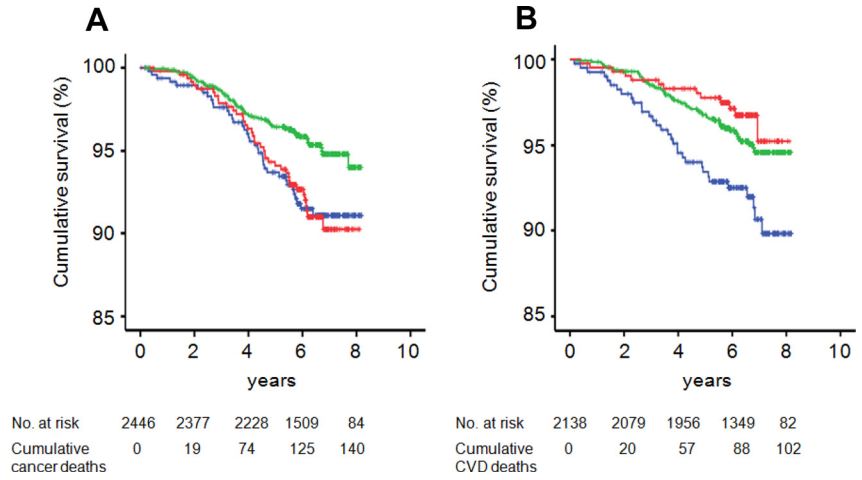


**FIG. 2.** Kaplan-Meier survival curves for cancer (A) and CVD (B) mortality by serum IGF-I concentration. In A, men with a history of cancer before baseline were excluded. In B, men with a history of CVD before baseline were excluded. *Blue* is low (quintile 1), *green* is intermediate (quintiles 2–4), and *red* is high (quintile 5) serum IGF-I concentration. $P$ = 0.001 and $P$ = 0.003, respectively, by log-rank test.

## Discussion

The results of a recent meta-analysis suggest a U-shaped association between serum IGF-I concentration and mortality from all causes (28). However, previous studies have not been able to define the distribution of cause-specific mortality underlying this association, possibly due to incomplete classification of causes of death, lack of sufficient statistical power, or the absence of nonlinear statistical approaches. Furthermore, other studies have observed gender differences in terms of the association between serum IGF-I and mortality (17, 19, 33). The present study is the first large-scale (n = 2901, deaths = 586) prospective study to evaluate the association between serum IGF-I concentration and cause-specific mortality in men. Herein, we demonstrate that low as well as high serum IGF-I levels associate with increased cancer mortal-

**TABLE 3.** HRs with 95% CIs of CVD mortality by quintiles of serum IGF-I concentration

| | Quintile 1 (<20th percentile) | Quintiles 2–4 (20–80th percentile) | Quintile 5 (>80th percentile) |
|---|---|---|---|
| CVD mortality | | | |
| Deaths [n (%)] | 57 (9.8) | 118 (6.8) | 39 (6.7) |
| Base model | 1.48 (1.08–2.04) | 1.0 (referent) | 1.07 (0.75–1.55) |
| Multivariate model A | 1.46 (1.06–2.03) | 1.0 (referent) | 1.02 (0.70–1.48) |
| Multivariate model B | 1.45 (1.04–2.02) | 1.0 (referent) | 0.92 (0.63–1.36) |
| Multivariate model C | 1.42 (1.02–1.98) | 1.0 (referent) | 0.88 (0.60–1.30) |
| CVD mortality with exclusions[a] | | | |
| Deaths [n (%)] | 32 (7.7) | 57 (4.4) | 13 (3.1) |
| Base model | 1.87 (1.21–2.90) | 1.0 (referent) | 0.75 (0.41–1.37) |
| Multivariate model A | 1.93 (1.24–2.99) | 1.0 (referent) | 0.73 (0.39–1.37) |
| Multivariate model B | 1.97 (1.26–3.01) | 1.0 (referent) | 0.66 (0.34–1.27) |
| Multivariate model C | 1.92 (1.22–3.00) | 1.0 (referent) | 0.63 (0.33–1.22) |

HRs were calculated using Cox proportional hazards regression. In the base model, adjustment was made for age, MrOS site, and time of serum sampling. Multivariate model A was adjusted for age, MrOS site, time of serum sampling, BMI (log-transformed), and quartile of physical activity (kilometers walked per day). Multivariate model B was adjusted for age, MrOS site, time of serum sampling, BMI (log-transformed), quartile of physical activity (kilometers walked per day), current smoking (yes/no), hypertension, and diabetes mellitus. Multivariate model C was adjusted for age, MrOS site, time of serum sampling, BMI (log-transformed), quartile of physical activity (kilometers walked per day), current smoking (yes/no), hypertension, diabetes mellitus, serum CRP (log-transformed), and ApoB to ApoA1 ratio.

[a] Men with a history of CVD at baseline were excluded.

ity, whereas only low levels associate with increased CVD mortality in older Swedish men.

We found that high serum IGF-I levels associated with increased cancer mortality. IGF-I participates in the regulation of mitogenesis and cellular differentiation (2). Experimentally induced overexpression of IGF-I in transgenic mice accelerates the onset and progression of some cancers (2). Some clinical studies suggest that high serum IGF-I levels associate with increased risk of cancer (*e.g.* colonic, prostate, and breast cancer) (4–6). GH excess in acromegaly is associated with an increased rate of colorectal cancer (7, 8). Furthermore, our results concur with a recent relatively small study of 633 men above 50 yr of age who participated in the Rancho Bernardo Study, which showed that high serum IGF-I levels associate with increased cancer mortality (cancer deaths, n = 74) (9). Our well-powered study (cancer deaths, n = 211) demonstrates that the risk of death from malignant disease almost doubled among elderly men with a serum IGF-I concentration in the highest quintile compared with men with serum IGF-I levels in the three intermediate quintiles. Together, both studies clearly establish high serum IGF-I concentration as a risk marker for cancer mortality in men.

In the present study, the association between serum IGF-I concentration and cancer mortality was nonlinear and U-shaped as demonstrated by restricted cubic spline Cox proportional hazard models. Thus, high as well as low serum IGF-I levels associated with increased cancer mortality. Although a previous study (cancer deaths, n = 107) showed an association between low serum IGF-I levels and increased cancer mortality in men (17), low levels of circulating IGF-I have not been significantly associated with increased risk of death from malignant diseases in other studies (18, 21, 34). Interestingly, several studies suggest increased incidence or mortality from malignant diseases in hypopituitary patients with severe GH deficiency (12, 35–37), but the underlying mechanisms remain unclear. Serum IGF-I is positively associated with variables reflecting general health status such as lean mass and nutritional intake (1). Therefore, the association between low serum IGF-I and increased cancer mortality could be confounded by the fact that men with early, undiagnosed tumors have a poor general health, resulting in low serum IGF-I concentrations. However, we adjusted the statistical analyses for men with a history of cancer before baseline, excluded men that deceased during the first 2 yr of follow-up, and adjusted for major prevalent diseases and multiple other covariates. Therefore, it is less likely that the association between low serum IGF-I and increased mortality from malignant diseases was confounded by men with low serum IGF-I values due to undiagnosed cancers. Future studies should determine whether different types of cancer underlie the associations between low and high IGF-I, respectively, and cancer death.

We found that low serum IGF-I levels associated with increased CVD mortality in elderly men. Previous studies addressing the association between serum IGF-I and CVD mortality have shown conflicting results, likely due to incomplete classification of causes of death, mixed study populations (*i.e.* both men and women), and lack of sufficient statistical power (21–23). However, some previous population-based studies have shown increased CVD mortality in subjects with low circulating IGF-I (17, 18, 20). Furthermore, hypopituitary patients with GH defi-

ciency and low serum IGF-I concentration display not only increased CVD mortality (10–12) but also subclinical inflammation, impaired cardiovascular performance, and premature atherosclerosis as possible mechanisms underlying the association between low IGF-I and CVD death (8). In prospective studies, low serum IGF-I concentration associated with increased risk of ischemic heart disease (13) and congestive heart failure (14). We believe that the present study provides strong additional evidence that low serum IGF-I levels do indeed associate with increased CVD mortality in elderly men.

A strength of the present study is that mortality data were obtained from the population statistics in Sweden, to which all deaths and causes of death in Sweden are reported, and there was no loss of follow-up. Furthermore, serum IGF-I concentration was measured using a well-established assay, and nonlinear associations between serum IGF-I concentration and mortality were determined using restricted cubic spline Cox proportional hazard models. A limitation is that self-reported questionnaires were used, and we cannot exclude the possibility that this could have resulted in an underestimation of the prevalence of current smoking and prevalent diseases. Furthermore, nonfatal CVD or cancer morbidity could have a closer temporal relationship with the measured serum IGF-I concentration than mortality from these diseases. Therefore, another limitation of the present study is that data regarding nonfatal CVD events and nonfatal cancer incidence during the follow-up were not available. In addition, comorbidity in both cancer and CVD at time of death could not be assessed. Finally, our results are based on single measurements of IGF-I and may therefore underestimate the true associations.

In conclusion, this is the first large-scale prospective study that has investigated the association between serum IGF-I concentration and cause-specific mortality in elderly men. Our results confirm a U-shaped relation between serum IGF-I concentration and all-cause mortality. We extend previous studies by showing that low serum IGF-I levels associate with increased cancer and CVD mortality, whereas high levels associate specifically with increased cancer mortality. These findings demonstrate that both low and high serum IGF-I levels are risk markers for cancer mortality in older Swedish men. More studies are needed to determine the mechanisms underlying these associations between serum IGF-I levels and cause-specific mortality in men. In particular, future studies should determine whether different types of cancer underlie the associations between low and high IGF-I, respectively, and cancer death.

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