Plasma YKL-40 and Total and Disease-Specific Mortality in the General Population

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BACKGROUND: Increased plasma YKL-40 is associated with short-term survival in patients with cardiovascular disease and cancer. We tested the hypothesis that increased plasma YKL-40 is associated with total and disease-specific mortality in the general population.

METHODS: We measured plasma YKL-40 in 8899 study participants, aged 20–95 years, in the Copenhagen City Heart Study from the Danish general population who were followed for 16 years: 3059 died, 2158 had ischemic cardiovascular disease, 2271 had cancer, and 2820 had other diseases associated with increased YKL-40. Hazard ratios for early death and absolute 10-year mortality rates were calculated according to plasma YKL-40 percentile groupings computed within sex and age decade: 0%–33%, 34%–66%, 67%–90%, 91%–95%, and 96%–100%.

RESULTS: Median survival age decreased from 83 years for participants with plasma YKL-40 in category 0%–33% to 69 years in category 96%–100% (trend, P < 0.0001). Risk of early death was increased (multifactorially adjusted hazard ratios) by 10% for YKL-40 category 34%–66%, by 30% for 67%–90%, by 70% for 91%–95%, and by 90% for 96%–100% vs YKL-40 category 0%–33% (trend, P < 0.0001). Corresponding increases in participants with ischemic cardiovascular disease were 10%, 20%, 50%, and 70% (P < 0.0001); in those with cancer were 10%, 20%, 50%, and 70% (P < 0.0001); and in those with other diseases were 10%, 20%, 40%, and 60% (P < 0.0001). Highest absolute 10-year mortality rates were 78% and 90% in women and men, respectively, who were >70 years old, smoked, and were in YKL-40 category 96%–100%.

CONCLUSIONS: Increased plasma YKL-40 is associated with risk of early death from cardiovascular disease, cancer, and other diseases in the general population.

YKL-40 (also named chitinase-3-like-1 and human cartilage glycoprotein-39) is an emerging new biomarker. Although increased plasma YKL-40 concentrations have been found to be associated with cancer (1), the role of this marker in cardiovascular disease (2) and all-cause mortality is unclear. We have recently shown that increased plasma YKL-40 concentrations in individuals from the general population were associated with increased risk of gastrointestinal cancer (3). YKL-40 has been regarded as an acute-phase protein, because its plasma concentration increases more than 25% after an inflammatory stimulus, but YKL-40 is different from and independent of C-reactive protein (CRP). Increased plasma YKL-40 concentrations have been seen in patients with diseases characterized by inflammation and ongoing tissue remodeling, such as ischemic cardiovascular diseases, cancer, diabetes, asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, inflammatory bowel disease, pneumonia, and liver fibrosis (1–7).

YKL-40 is a member of the family of mammalian chitinase-like proteins and is a highly conserved protein (1, 4, 8). YKL-40 is mainly produced by macrophages, neutrophils, and cancer cells (1, 4, 6, 7, 9–11). YKL-40 has roles in cell proliferation and differentiation (12), angiogenesis (13–15), inflammation (1–7, 16, 17), remodeling of the extracellular matrix (1, 4, 18, 19), and the innate immune response (6, 20). This protein also protects against apoptosis (17).

We tested the hypothesis that increased plasma YKL-40 concentrations are associated with total and

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Plasma YKL-40 and Early Death

For regression dilution bias, the inclusion of these individuals allowed us to correct for disease at the 1991–1994 and 2001–2003 examinations. The participants who were selected had no known examination of the Copenhagen City Heart Study cohort. The participants filled out a self-administered questionnaire, which was validated by the participant and an investigator on the day of attendance. Participants reported on smoking habits for pack-year calculation and were subdivided into never, previous, and current smokers. Participants also reported on weekly alcohol consumption (g), and on physical activity at work and during leave time; physical activity <4 h weekly was considered light exercise. Body mass index (kg/m²) and systolic blood pressure were measured by an examiner. Plasma cholesterol (Boehringer Mannheim) and high-sensitivity CRP (Dako) were measured on an autoanalyzer.

Methods

Participants
We recruited study participants from the group of individuals who were participating in a population-based, prospective study of the Danish general population, the 1991–1994 examination of the Copenhagen City Heart Study (21–23). Participants age 20 years and older were selected randomly after sex and age stratification into 5-year groups among residents of Copenhagen. Of 17180 individuals invited, 10135 participated, and plasma samples from 8899 participants were available for YKL-40 determination. Each participant was followed in the Danish health registries through July 2007. Follow-up was 100% complete at the time of this report. Roughly 99% of participants were white and of Danish descent.

Plasma YKL-40 was measured a second time in blood samples from 929 participants of the 2001–2003 examination of the Copenhagen City Heart Study cohort. The participants who were selected had no known disease at the 1991–1994 and 2001–2003 examinations. The inclusion of these individuals allowed us to correct for regression dilution bias (24).

End Points
We collected information on mortality and morbidity from 3 different population registries by using the participants’ unique national Danish Central Person Registry numbers. Information on mortality (from baseline through July 2007) was obtained from the national Danish Civil Registration System (25). Information on diagnoses of cancer was obtained from the national Danish Cancer Registry (from 1947 through 2004) (26) and the national Danish Patient Registry (from 2004 through July 2007). Information on other morbidity (from 1976 through July 2007) known to be associated with increased plasma YKL-40 (ischemic cardiovascular disease, diabetes, chronic obstructive pulmonary disease, asthma, rheumatoid arthritis, inflammatory bowel disease, pneumonia, and benign liver disease) was obtained from the national Danish Patient Registry.

Ethics
All participants gave written informed consent. The study was approved by Herlev Hospital and the Copenhagen and Frederiksberg ethics committee (No. 100.2039/91 and 01–144/01), and conducted in accordance with the Declaration of Helsinki.

YKL-40 Analysis
Plasma concentrations of YKL-40 were measured in duplicate by use of a commercial ELISA (Quidel) in samples that had been frozen for 12–15 years at −80 °C. The detection limit was 20 μg/L. The intraassay CVs were 5% (at 40 μg/L), 4% (at 104 μg/L), and 4% (at 155 μg/L). The interassay CV was <6%. YKL-40 is stable for at least 15 years in plasma samples stored at −80 °C (personal observation).

Other Covariates
The participants filled out a self-administered questionnaire, which was validated by the participant and an investigator on the day of attendance. Participants reported on smoking habits for pack-year calculation and were subdivided into never, previous, and current smokers. Participants also reported on weekly alcohol consumption (g), and on physical activity at work and during leave time; physical activity <4 h weekly was considered light exercise. Body mass index (kg/m²) and systolic blood pressure were measured by an examiner.

Statistical Analysis
We used Stata version 10.1 (Stata Corp LP). Two-sided P < 0.05 was considered significant. Mann–Whitney rank-sum and Pearson χ² tests were used. Plasma YKL-40 concentrations increase with increasing age, so instead of using the measured plasma YKL-40 concentration in the statistical analysis, we categorized participants into 5 different percentile groups (0%–33%, 34%–66%, 67%–90%, 91%–95%, and 96%–100%) by sex and age group (<30, 30–39, 40–49, 50–59, 60–69, 70–79, and ≥80 years) at the time of blood sampling. Each percentile group thus contained participants of all ages and both sexes. These groups were prespecified so that tertiles in the lower range and extreme phenotypes in the upper range were both evaluated (27). For some analyses the 5 groups were combined into 3 percentile categories (0%–33%, 34%–90%, and 91%–100%) to increase statistical power.

Cumulative survival against left-truncated age and follow-up time in all participants was assessed by using Kaplan–Meier plots. Kaplan–Meier plots also were used in analysis of cumulative survival in subgroups of participants with ischemic cardiovascular disease, cancer, and other diseases (diabetes, chronic obstructive pulmonary disease, asthma, rheumatoid arthritis, inflammatory bowel disease, pneumonia, and benign liver disease) as a function of follow-up time. Differences...
between plasma YKL-40 percentile categories were examined by using log-rank tests. Standardized mortality rates were calculated per 10 000 person-years, by using the WHO standard population (28) to adjust for any variations in age composition of participant subgroups. Hazard ratios and 95% CIs for early death were calculated by using Cox regression analysis and adjusted for all risk factors at the time of blood sampling, as listed in Table 1. Hazard ratios were multifactorially adjusted for sex (dichotomous), age (deciles), smoking habits (never/previous/current smokers), body mass index (continuous), alcohol consumption (continuous), plasma cholesterol (continuous), systolic blood pressure (continuous), physical activity (dichotomous), CRP (continuous), and earlier diseases at the time of blood sampling (dichotomous). For trend tests, increasing plasma YKL-40 categories labeled 0, 1, 2, 3, and 4 (5 categories) or 0, 1, and 2 (3 categories) were used as a continuous variable in the Cox regression. P values for the trend test were calculated by using the χ² value (1 degree of freedom) of the likelihood-ratio test of the model without plasma YKL-40 categories nested within the model with plasma YKL-40 categories. We tested for proportionality of hazards over time based on Schöenfeld residuals and found no major violations. Information on baseline covariates was more than 99% complete, except for body mass index; individuals for whom information on covariates was incomplete were excluded from the multifactorial analysis. Hazard ratios were also corrected for regression dilution bias by using a nonparametric method (24). For this correction we used plasma YKL-40 from 929 healthy individuals who attended both the 1991–1994 baseline and the 2001–2003 follow-up examinations. A regression dilution ratio of 0.8042 was computed. Absolute 10-year mortality according to plasma YKL-40 percentile categories was estimated by using the regression coefficients from a Poisson regression model including the following covariates: sex, age (<30, 30 to <40, 40 to <50, 50 to <60, 60 to <70, and ≥70 years), and smoking habits (never, previous, and current smokers) at the time of blood sampling. Absolute mortality is presented as estimated incidence rates (events per 10 years) in percentages.

### Results

The study population consisted of 8899 participants (56% women, age 20–95 years, mean 59 years). Plasma YKL-40 concentrations increased with increasing age, as illustrated in Fig. 1. Baseline characteristics of all participants according to plasma YKL-40 percentile categories adjusted for age and sex are given in Table 1. Increasing plasma YKL-40 concentrations were associ-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>0%–33%</th>
<th>34%–66%</th>
<th>67%–90%</th>
<th>91%–95%</th>
<th>96%–100%</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>2964 (33)</td>
<td>2932 (33)</td>
<td>2121 (24)</td>
<td>445 (5)</td>
<td>437 (5)</td>
<td>–</td>
</tr>
<tr>
<td>Women, %</td>
<td>57</td>
<td>56</td>
<td>56</td>
<td>56</td>
<td>57</td>
<td>0.96</td>
</tr>
<tr>
<td>Age, years</td>
<td>61 (48–71)</td>
<td>61 (48–71)</td>
<td>61 (48–71)</td>
<td>60 (48–71)</td>
<td>61 (48–71)</td>
<td>0.12</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>43</td>
<td>48</td>
<td>51</td>
<td>56</td>
<td>58</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total tobacco consumption, pack-years</td>
<td>15 (0–32)</td>
<td>19 (1–35)</td>
<td>22 (3–38)</td>
<td>24 (5–40)</td>
<td>26 (9–45)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m²²</td>
<td>24.6 (22.3–27.3)</td>
<td>24.9 (22.5–28.0)</td>
<td>25.1 (22.5–28.1)</td>
<td>25.3 (22.7–28.2)</td>
<td>24.9 (22.0–28.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Alcohol, g/week</td>
<td>48 (0–120)</td>
<td>60 (12–144)</td>
<td>72 (24–180)</td>
<td>108 (24–240)</td>
<td>156 (48–360)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plasma cholesterol, mmol/L</td>
<td>6.0 (5.2–6.9)</td>
<td>6.2 (5.4–7.1)</td>
<td>6.2 (5.3–7.1)</td>
<td>6.1 (5.4–6.9)</td>
<td>5.8 (4.9–6.7)</td>
<td>0.52</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>135 (121–150)</td>
<td>136 (122–152)</td>
<td>139 (124–155)</td>
<td>140 (125–157)</td>
<td>141 (125–159)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Physically inactive, %</td>
<td>13</td>
<td>13</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>1.5 (1.2–2.3)</td>
<td>1.7 (1.3–2.8)</td>
<td>2.1 (1.4–4.1)</td>
<td>2.3 (1.5–5.0)</td>
<td>2.4 (1.4–4.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cancer, %</td>
<td>7</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>11</td>
<td>0.02</td>
</tr>
<tr>
<td>Ischemic cardiovascular disease, %</td>
<td>6</td>
<td>7</td>
<td>9</td>
<td>8</td>
<td>10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other diseases, %b</td>
<td>5</td>
<td>7</td>
<td>9</td>
<td>11</td>
<td>15</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Values were collected at the 1991 through 1994 examination of the Copenhagen City Heart Study, and are expressed as number, percent, or median (interquartile range). Statistical comparisons between the five YKL-40 percentile categories were made using trend test (YKL-40 categories were coded 0, 1, 2, 3, and 4 for increasing percentile categories).

b Other diseases: diabetes, chronic obstructive pulmonary disease, asthma, rheumatoid arthritis, inflammatory bowel disease, pneumonia, and benign liver disease.
ated with smoking, high alcohol consumption, high systolic pressure, physical inactivity, and high CRP (all trend, \( P < 0.0001 \)). Patients with known cancer, ischemic cardiovascular disease, and other diseases (i.e., diabetes, chronic obstructive pulmonary disease, asthma, rheumatoid arthritis, inflammatory bowel disease, pneumonia, and benign liver disease) were found in all YKL-40 percentile categories, but more were seen in the highest categories (Table 1).

**PLASMA YKL-40 AND TOTAL MORTALITY IN THE GENERAL POPULATION**

During the 16 years of follow-up, 3059 of the 8899 participants died. Increasing plasma YKL-40 concentrations (divided into 5 sex and 10-year age percentile categories) were associated with increasing risk of early death (log-rank trend, \( P < 0.0001 \)) (Fig. 2). Median (95% CI) survival age was 83 (82–84) years for plasma YKL-40 concentrations in category 0%–33%, 81 (80–82) years for 34%–66%, 78 (77–80) years for 67%–90%, 73 (69–75) years for 91%–95%, and 69 (66–72) years for category 96%–100%. Corresponding 15-year survival rates in these 5 plasma YKL-40 categories were 70% (68%–71%), 66% (64%–67%), 59% (57%–62%), 52% (47%–58%), and 44% (39%–49%) (Table 2). Men had lower median survival age and lower 15-year survival rates than women in all plasma YKL-40 categories. The effect on median survival age and 15-year survival rates of increasing plasma YKL-40 concentrations was similar to or even higher than that of current vs never smoking status (Fig. 2, Table 2). The standardized mortality rate per 10 000 person-years was highest in men with plasma YKL-40 concentrations in the category 96%–100%. If we included in the analysis only participants without diagnosis of cancer, ischemic cardiovascular disease, or other diseases at the time of blood sampling, similar results were found (see Table 1 in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol56/issue10).

For plasma YKL-40–concentration percentile categories, risk of early death was increased (multifactorially adjusted for sex, age, smoking habits, body mass index, alcohol consumption, plasma cholesterol, systolic blood pressure, physical activity, CRP, and earlier diseases at time of blood sampling) by 10% (hazard ratio 1.1, 95% CI 1.0–1.2) for plasma YKL-40 concentrations in percentile category 34%–66%, by 30% (1.3, 1.2–1.4) for 67%–90%, by 70% (1.7, 1.5–2.0) for 91%–95%, and by 90% (1.9, 1.6–2.2) for 96%–100% vs plasma YKL-40 concentrations in percentile category 0%–33% (trend, \( P < 0.0001 \)) (Table 3). These estimates remained constant after we excluded data for participants who suffered violent death (n = 71).
We also examined whether plasma YKL-40 concentration was associated with risk of early death in participants with low or high plasma CRP concentrations (Table 3). In the 4371 participants with CRP ≤1.75 mg/L, the hazard ratios for early death were 1.0 (95% CI 0.9–1.2) for plasma YKL-40 concentrations in percentile category 34%–66%, 1.3 (1.1–1.5) for 67%–90%, 1.8 (1.4–2.5) for 91%–95%, and 2.2 (1.7–3.0) for 96%–100% vs plasma YKL-40 concentrations in percentile category 0%–33% (trend, P = 0.0001). Similar results were found in participants with plasma CRP >1.75 mg/L (trend, P < 0.0001), in never smokers (trend, P < 0.0001), and in ever smokers (trend, P < 0.0001).

**ABSOLUTE 10-YEAR MORTALITY**

The lowest absolute 10-year mortality was 0.1% in never-smoking women aged <30 years in the plasma YKL-40 percentile category 0%–33% (Fig. 3). Absolute 10-year mortality was higher in men than in women and increased with increasing age and from never through previous to current smoking status. The highest absolute 10-year mortality was 78% and 90% in smoking women and men aged >70 years, respectively, and in the 96%–100% plasma YKL-40 percentile category (Fig. 3).

**PLASMA YKL-40 CONCENTRATION AND DISEASE-SPECIFIC MORTALITY**

In participants who developed ischemic cardiovascular disease, cancer, and other diseases before or during follow-up, risk of early death also increased with increasing plasma YKL-40 concentrations (Table 3). Risk of early death was increased by 10% [hazard ratios were multifactorially adjusted for sex, age (deciles), and...
smoking habits (never/previous/current smokers), body mass index, alcohol consumption, plasma cholesterol, systolic blood pressure, physical activity, CRP, and earlier diseases at the time of blood sampling] in participants with cardiovascular disease for plasma YKL-40 concentrations in category 34%–66%, by 20% for 67%–90%, by 80% for 91%–95%, and by 60% for 96%–100% vs YKL-40 category 0%–33% (trend, \( P < 0.0001 \)). Corresponding increases in participants with cancer were 10%, 20%, 50%, and 70% (trend, \( P < 0.0001 \)), and in participants with other diseases were 10%, 20%, 40%, and 60% (trend, \( P < 0.0001 \)).

Online Supplementary Table 2 gives the risk of early death with increasing plasma YKL-40 concentrations after adjustment for regression dilution bias. Online Supplementary Table 3 gives the risk of early death with increasing plasma YKL-40 concentrations in study participants with cancer, ischemic cardiovascular disease, and other diseases stratified in those whose disease was diagnosed after blood sampling.

In participants with ischemic cardiovascular disease at inclusion and follow-up, those with plasma YKL-40 concentrations in percentile category 91%–100% had a median survival time after blood sampling of 9 years (74% cumulative survival after 5 years) vs 13 years (83% cumulative survival after 5 years) for those with plasma YKL-40 concentrations in percentile category 0%–33% (trend, \( P < 0.0001 \)). The corresponding multifactorially adjusted hazard ratio for early death was 1.7 (1.4–2.1). Similar results were found if only data from participants with prevalent ischemic cardiovascular disease were included in the analysis (Fig. 5).

In participants with cancer at inclusion and follow-up, those with plasma YKL-40 concentrations in percentile category 91%–100% had a median survival time after blood sampling of 9 years (82% cumulative survival after 5 years) vs 13 years (92% cumulative survival after 5 years) for those with plasma YKL-40 concentrations in percentile category 0%–33% (trend, \( P < 0.0001 \)). The corresponding multifactorially adjusted hazard ratio for early death was 1.6 (1.3–2.0). Similar results were found if only data from participants with prevalent cancer were included in the analysis (Fig. 5).

In participants with other diseases (diabetes, chronic obstructive pulmonary disease, asthma, rheumatoid arthritis, inflammatory bowel disease, pneumonia, and benign liver disease) at inclusion and follow-up, those with plasma YKL-40 concentrations in percentile category 91%–100% had a median survival time after blood sampling of 11 years (79% cumulative survival after 5 years) vs 14 years (89% cumulative survival after 5 years) for those in plasma YKL-40 percentile category 0%–33% (trend, \( P < 0.0001 \)). The corresponding multifactorially adjusted hazard ratio for early death was 1.8 (1.6–2.1). Similar results were found if only data from participants with prevalent other diseases were included in the analysis (Fig. 5).

**Table 2.** Median survival age, 15-year survival, and standardized mortality rate in 8899 participants from the general population according to plasma YKL-40 percentile category or smoking status.a

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Median survival age (95% CI), years</th>
<th>15-Year survival (95% CI), %</th>
<th>Standardized mortality rate per 10 000 person-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>YKL-40 percentile category</td>
<td>All</td>
<td>Men</td>
<td>All</td>
</tr>
<tr>
<td>0%–33%</td>
<td>83 (82–84)</td>
<td>85 (84–86)</td>
<td>80 (78–82)</td>
</tr>
<tr>
<td>34%–66%</td>
<td>81 (80–82)</td>
<td>84 (83–85)</td>
<td>77 (75–79)</td>
</tr>
<tr>
<td>67%–90%</td>
<td>78 (76–79)</td>
<td>82 (81–83)</td>
<td>73 (71–75)</td>
</tr>
<tr>
<td>91%–95%</td>
<td>72 (71–73)</td>
<td>77 (75–79)</td>
<td>68 (67–70)</td>
</tr>
<tr>
<td>96%–100%</td>
<td>69 (69–70)</td>
<td>74 (72–76)</td>
<td>66 (65–68)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Never</td>
<td>Previous</td>
<td>Current</td>
</tr>
<tr>
<td>0%–33%</td>
<td>87 (86–88)</td>
<td>87 (86–88)</td>
<td>85 (84–86)</td>
</tr>
<tr>
<td>34%–66%</td>
<td>82 (81–83)</td>
<td>86 (85–87)</td>
<td>85 (84–86)</td>
</tr>
<tr>
<td>67%–90%</td>
<td>78 (77–79)</td>
<td>82 (81–83)</td>
<td>81 (80–82)</td>
</tr>
<tr>
<td>91%–95%</td>
<td>71 (70–72)</td>
<td>75 (74–76)</td>
<td>71 (70–72)</td>
</tr>
</tbody>
</table>

a Based on 8899 participants from the Copenhagen City Heart Study 1991–1994 examination followed for 16 years. Mortality rate was standardized according to the WHO standard population (www.who.int/entity/healthinfo/paper31.pdf) [Ahmad et al. (28)].
<table>
<thead>
<tr>
<th>Population</th>
<th>Participants/ events</th>
<th>Multifactorially adjusted hazard ratio by sex and 10-year age-group percentile of YKL-40 (95% CI)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0%–33%</td>
<td>34%–66%</td>
</tr>
<tr>
<td>All</td>
<td>8616/2840</td>
<td>1.0</td>
<td>1.1 (1.0 to 1.2)</td>
</tr>
<tr>
<td>Plasma CRP ≤1.75 mg/L</td>
<td>4371/1029</td>
<td>1.0</td>
<td>1.0 (0.9 to 1.2)</td>
</tr>
<tr>
<td>Plasma CRP &gt;1.75 mg/L</td>
<td>4245/1811</td>
<td>1.0</td>
<td>1.2 (1.0 to 1.3)</td>
</tr>
<tr>
<td>Never smokers</td>
<td>1977/415</td>
<td>1.0</td>
<td>1.0 (0.8 to 1.3)</td>
</tr>
<tr>
<td>Ever smokers</td>
<td>6639/2425</td>
<td>1.0</td>
<td>1.1 (1.0 to 1.3)</td>
</tr>
<tr>
<td>Participants with cancer</td>
<td>2197/1334</td>
<td>1.0</td>
<td>1.1 (1.0 to 1.3)</td>
</tr>
<tr>
<td>Participants with ischemic cardiovascular disease</td>
<td>2049/1225</td>
<td>1.0</td>
<td>1.1 (1.0 to 1.3)</td>
</tr>
<tr>
<td>Participants with other diseases</td>
<td>2682/1481</td>
<td>1.0</td>
<td>1.1 (0.9 to 1.2)</td>
</tr>
<tr>
<td>Participants with cancer at baseline</td>
<td>667/379</td>
<td>1.0</td>
<td>1.3 (1.0 to 1.7)</td>
</tr>
<tr>
<td>Participants with ischemic cardiovascular disease at baseline</td>
<td>608/420</td>
<td>1.0</td>
<td>1.2 (0.9 to 1.6)</td>
</tr>
<tr>
<td>Participants with other diseases at baseline</td>
<td>596/353</td>
<td>1.0</td>
<td>1.0 (0.8 to 1.4)</td>
</tr>
</tbody>
</table>

*a Numbers of participants vary slightly depending for availability of data. Total number of participants is slightly lower than 8899 due to lack of complete phenotypical information on 383 participants.

*b Hazard ratios were multifactorially adjusted for sex (dichotomous), age (deciles), smoking habits (never/previous/current smokers), body mass index (continuous), alcohol consumption (continuous), plasma cholesterol (continuous), systolic blood pressure (continuous), physical activity (dichotomous), CRP (continuous), and earlier diseases at the time of blood sampling (dichotomous). Corresponding hazard ratios also adjusted for regression dilution bias are given in online Supplementary Table 1.

*c Includes participants with disease prior to and after baseline. Corresponding values stratified on the basis of disease diagnosis after blood sampling (= baseline) are given in online Supplementary Table 3.

*d Other diseases: diabetes, chronic obstructive pulmonary disease, asthma, rheumatoid arthritis, inflammatory bowel disease, pneumonia, and benign liver disease. Some participants had more than 1 disease.
adjusted hazard ratio for early death was 1.5 (1.3–1.8). Similar results were found if only data from participants with prevalent other diseases were included in the analysis (Fig. 5).

Discussion

In this study of adults from the Danish general population we found that increased plasma YKL-40 concentration was associated with risk of early death, because of deaths from cardiovascular diseases and cancer as well as other diseases. We observed a 14-year difference in median survival age between participants with extremely high plasma YKL-40 concentrations (96%–100% percentile category) vs participants with the lowest plasma YKL-40 concentrations (0%–33% percentile category). Furthermore, the risk of early death was increased by 90% for participants with extremely high plasma YKL-40 concentrations, and in this group absolute 10-year mortality was 78% and 90% in female and male smokers >70 years old, respectively. The association between increasing plasma YKL-40 concentrations and increasing risk of early death was similar to or higher than that of smoking status, and the plasma YKL-40 percentile category was a risk factor for early death independent of age, sex, smoking status, body mass index, alcohol consumption, plasma cholesterol, systolic blood pressure, physical activity, plasma CRP, and earlier diseases present at the time of blood sampling (i.e., cancer, ischemic cardiovascular disease, diabetes, chronic obstructive pulmonary disease, asthma, rheumatoid arthritis, inflammatory bowel disease, pneumonia, and benign liver disease). These are all novel observations.

The mechanism behind the increased risk of early death in participants with increased plasma YKL-40 concentrations is not completely clear. It remains to be established whether YKL-40 plays a role in the pathogenesis of ischemic cardiovascular diseases, cancer, and other diseases characterized by inflammation and tissue remodeling, whether these diseases lead to increased plasma YKL-40, or whether inflammation, tissue remodeling or some other factors cause both increased plasma YKL-40 and these diseases.

One interpretation of our data is that plasma YKL-40 concentrations reflect the severity of ischemic cardiovascular diseases, cancer, and other diseases because individuals with the highest plasma concentrations of YKL-40 had the highest risk of early death. YKL-40 participates in inflammatory processes, angio-
genesis, tissue destruction/remodeling, and apoptosis (1–7, 9–20), factors important for progression in disease severity in ischemic cardiovascular diseases and other diseases. Cancer cells with high production of YKL-40 may have an aggressive phenotype with a high proliferation/differentiation rate and metastatic poten-

Fig. 4. Survival according to plasma YKL-40 percentile categories in participants with cancer, ischemic cardiovascular disease and other diseases at inclusion and follow-up.

YKL-40 concentrations were divided into 3 sex and 10-year age percentile categories: 0–33%, 34–90%, and 91–100%. Follow-up began at time of blood sampling and ended at death or July 2007, whichever came first. Hazard ratios were multifactorially adjusted for sex, age (deciles), and smoking habits (never/previous/current smokers), body mass index, alcohol consumption, plasma cholesterol, systolic blood pressure, physical activity, CRP, and earlier diseases at the time of blood sampling. P values are from tests for log-rank trend. Some participants had more than 1 disease.
tial, factors associated with short survival. In support of
this theory, increased plasma YKL-40 concentration
was associated with increased risk of gastrointestinal
cancer, a type of cancer that often grows to large size
and metastasizes before it is diagnosed (3).

YKL-40 is an acute-phase protein (4). In contrast
to CRP, which is mainly produced by hepatocytes in
response to high interleukin-6 concentrations, the in-
crease in plasma YKL-40 originates directly from in-
flammatory cells and cancer cells (1, 4) and may there-
fore be a more direct monitor of disease activity.

Because minor increases in plasma CRP associate with
early death in both healthy and diseased individuals
(29, 30) and therefore may have potentially con-

**Fig. 5.** Survival according to plasma YKL-40 percentile categories in participants with prevalent cancer, prevalent ischemic cardiovascular disease, and prevalent other diseases.

YKL-40 concentrations were divided into 3 sex and 10-year age percentile categories: 0%–33%, 34%–90%, and 91%–100%. Follow-up began at time of blood sampling and ended at death or July 2007, whichever came first. Hazard ratios were
multifactorially adjusted for sex, age (deciles), and smoking habits (never/previous/current smokers), body mass index, alcohol
consumption, plasma cholesterol, systolic blood pressure, physical activity, CRP, and earlier diseases present at the time of blood
sampling. P values are from tests for log-rank trend. Some participants had more than 1 disease.
founded our results, we also examined the association of increased plasma YKL-40 concentrations with early death selectively in participants with low plasma CRP (≥1.75 mg/L). Even in these individuals, the hazard ratios for early death increased significantly with increasing plasma YKL-40 concentrations, which suggests that the association of increased plasma YKL-40 with early death is independent of the association of increased plasma CRP.

A limitation of the present study was that the study population included only white participants, and our results may not apply to other ethnic groups. Another limitation was that individuals could participate only if they survived to the time of recruitment and blood sampling in 1991–94; thus we excluded individuals who died early in the Copenhagen City Heart Study (initiated in 1976–1978). A third limitation was that because of low numbers in our cohort of diseases characterized by inflammation and tissue remodeling, we could not examine the possible association between increased plasma YKL-40 concentration and risk of early death in these patients. A strength of the study was that the prognostic value of plasma YKL-40 was evaluated in a large cohort of well-characterized individuals, with a long follow-up period, and with no losses to follow-up.

In conclusion, in this large study of participants from the general population, we found a strong association between increased plasma YKL-40 concentration and risk of early death from cardiovascular diseases and cancer as well as other diseases, and this association was independent of plasma CRP concentration and smoking status. It remains to be determined whether routine measurement of plasma YKL-40 can provide useful clinical information for risk assessment in patients with ischemic cardiovascular disease, cancer, or other chronic inflammatory diseases, or for monitoring patients after intervention with different therapies.

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