Mortality rate from early prostate cancer increased 3-fold after 15 years following the diagnosis

Johansson JE, Andrén O, Andersson SO, et al. **Natural history of early, localized prostate cancer.** JAMA. 2004;291:2713-9.

QUESTION

In men with early prostate cancer (T0–T2 NX M0 classification), what is the prognosis for survival beyond 15 years?

METHODS

Design: Inception cohort followed for mean 21 years.

Setting: Central Sweden.

Patients: 223 men with early initially untreated prostate cancer (mean age at diagnosis 72 y).

Prognostic factors: Follow-up period; age at diagnosis; grades of tumors corresponding to the World Health Organization classification of malignant diseases, including grade 1 (highly differentiated), grade 2 (moderately differentiated), and grade 3 (poorly differentiated); and tumor stages corresponding to the TNM classification from 1978, including T01 (localized cancer in < 25% of the total specimen), T0d (diffuse cancer in ≥ 25% of the total specimen), and T1–T2 (confined to the prostate gland, with T1 indicating a nodule surrounded by normal prostate tissue and T2 indicating a large nodule or multiple nodules).

Outcomes: Progression of disease, and death from prostate cancer and all-cause mortality.

MAIN RESULTS

21.5% of the cohort was followed for > 15 years. At diagnosis, 52.5% had stage T1–T2 disease; 66.4% had grade 1 and 4% had grade 3 pathologic disease. Progression of cancer occurred in 40%, and generalized cancer occurred in 17% of patients. 91% of patients died; prostate cancer was considered the cause of death in 16% of the entire cohort. Prostate cancer mortality rate was greater after 15 years of follow-up than during the first 15 years (44 vs 15 deaths/1000 person-y, $P = 0.01$). Multivariable analysis showed that the risk for death from prostate cancer was greater after 15 years of follow-up than during the first 5 years and was greater among patients with grade 3 tumors than among those with grade 1 tumors (Table). Age at diagnosis and tumor stage were not associated with prostate cancer mortality (Table). None of the prognostic factors were strongly associated with local progression of disease (Table).

CONCLUSIONS

In men with early prostate cancer, the mortality rate from cancer increased 3-fold after 15 years of follow-up. Poorly differentiated tumors were also associated with an increased risk for death from cancer.

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Association between prognostic factors and prostate cancer mortality or local progression of the disease at mean 21-year follow-up*

Prognostic factors	Comparisons	Mortality Relative risk (95% CI)	Local progression Relative risk (CI)
Follow-up (y)	5 to 9 vs 0 to 4	2.2 (0.9 to 5.5)	0.6 (0.3 to 1.1)
	10 to 14 vs 0 to 4	2.0 (0.6 to 6.3)	0.6 (0.3 to 1.3)
	≥ 15 vs 0 to 4	6.4 (2.3 to 17.8)	0.8 (0.3 to 2.1)
Age at diagnosis (y)	≥ 70 vs < 70	0.7 (0.3 to 1.6)	0.9 (0.6 to 1.5)
Grades of tumors	2 vs 1	3.4 (1.6 to 7.3)	2.5 (1.6 to 4.0)
(WHO classification of malignant diseases)	3 vs 1	46.6 (12.3 to 177.4)	3.3 (0.9 to 11.9)
Tumor stages (TNM classification from 1978)	T0d vs T01	0.7 (0.2 to 2.1)	2.0 (0.9 to 4.4)
	T1–T2 vs T01	0.7 (0.3 to 1.6)	2.7 (1.5 to 4.9)

*CI defined in Glossary. WHO = World Health Organization.

COMMENTARY

The unique study by Johansson and colleagues describes the long-term outcomes of men diagnosed with prostate cancer before the era of prostate-specific antigen (PSA) screening and followed without attempted curative therapy. The study had high internal validity, although the use of androgen deprivation as the disease progressed was not fully reported. However, its generalizability to men diagnosed with prostate cancer in the "PSA era," as noted by the authors, is problematic.

For the minority of men diagnosed with poorly differentiated cancer or with rapidly rising PSA levels, it is unclear whether such local treatments as radical prostatectomy or radiation can change outcomes (1). However, for most men with well- or moderately differentiated cancer, this study suggests that prostate cancer mortality, and therefore the benefit of attempted curative therapy, is relatively low for 15 years, even without the effect of the considerable "lead time" of PSA as well as the substantial overdiagnosis, through PSA testing, of prostate cancer not destined to cause mortality.

Most prostate cancer guidelines suggest reserving PSA testing and attempted curative treatment for men with ≥ 10 years of life expectancy, or about 75 years of age for men with average comorbid conditions. In fact, if we accept the authors' assumption that about half of the prostate cancer deaths in this cohort might have been prevented by surgery, the number of men who would need to receive radical prostatectomy to prevent a prostate cancer death over 21 years would be about 9 for men < 70 years of age, compared with about 19 for men > 70 years of age. However, men spared a prostate cancer death would be at high risk for death from other causes over the short term in light of their age.

Perhaps, given these results, physicians should think twice about early detection and aggressive treatment efforts for men with less than a 15-year life expectancy or those older than 70 years of age with usual comorbid conditions. The effect of lead time and overdiagnosis in the PSA era might reasonably drive this life expectancy threshold even higher.

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Reference

1. **D'Amico AV, Chen MH, Roehl KA, Catalona WJ.** Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. N Engl J Med. 2004;351:125-35.