Title
Re: Radical Prostatectomy Versus Watchful Waiting in Early Prostate Cancer

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Re: Association of Statin Use with Pathological Tumor Characteristics and Prostate Cancer Recurrence After Surgery

Mondul AM, Han M, Humphreys EB, et al

J Urol 2011;185:1268–73

Expert's summary:

In this retrospective study of 2399 patients who underwent radical prostatectomy between 1993 and 2006, the primary and secondary preventive use of statins was evaluated. Using a retrospective cohort design, the outcome was calculated using Cox proportional hazard regression including recurrence. Covariates were intake of aspirin, angiotensin-converting enzyme inhibitors, and diabetic medications.

Mondul et al found that 16.1% of patients on statins at prostatectomy were 34% less likely to harbor a locally advanced cancer. Statin intake reduced the risk of a Gleason score $\geq$4 + 3 by 65% when the prostate-specific antigen (PSA) level was $\geq$10 ng/ml, but not at PSA $<$10 ng/ml. When statins were taken for $\geq$1 yr, the recurrence was reduced by 33%.

Expert's comments:

At a time when the incidence of prostate cancer has reached almost epidemic dimensions, means to reduce the number of men affected by the disease gain relevance. The high prevalence of this neoplasm and should stimulate ways and means to reduce its clinical manifestations. Dietary and chemoprevention came into focus with the Hirayama study [1]. Later, three phase-3 trials tested 5-α-reductase inhibitors and selenium plus vitamin E for chemoprevention of prostate cancer [2]. The preventive strategies studied by Hirayama successful, but are not accepted by aging men, whereas the latter studies failed [2]. Incidentally, other compounds like metformin, aspirin, and statins appear to prevent prostate cancer. This second mode of action, however, is not supported by prospective, randomized studies thus far. At any rate, since 2004, the action of statins on prostate cancer increasingly gained interest [3].

This well-designed retrospective study by Mondul et al supports the notion that statins have a chemopreventive effect on prostate cancer. An inverse association with statin intake was found apart from high-grade disease in men with a preoperative PSA $>$10 ng/ml, independent of the PSA level with non-organ-confined disease and the postoperative PSA level. Among statin users, age was unrelated to the local extent of the tumor, but in men $<$60 yr, the risk of recurrence was studied. Using a statin for at least a year after surgery lowered the risk of recurrence in general by 33% in this group; the rate of biochemical recurrence was reduced by 12%.

Why statins interfere with the development of prostate cancer is not clear. Their pleiotropic anti-inflammatory effects are mediated via peroxisome proliferator-activated receptors, in part, in the anticarcinogenic actin [4]. Interference with a complex mechanism of signal transduction using the protein kinase AKT is among six pathways in which nuclear factor kappa B is involved, as well [5].

Covariates of statin action might share in the chemopreventive effect; this was assessed in the Mondul et al study. It was found that body mass index, which is involved in a variety of ways in prostate cancer, did not modify statin action. Among medicines taken by the patients, aspirin reduced high-grade disease by 37% in concert with statins. Although diabetic medicines were studied, metformin was not specifically looked at.

This study has widened our focus on prostate cancer prevention by looking at the medications taken by many men.

Conflicts of interest: Jens E. Altwein has received lecture honoraria from AstraZenica and Takeda.

References

[1] Hirayama T. Epidemiology of prostate cancer with special reference to the role of diet. Natl Cancer Inst Monogr 1979;53:149–55.
[2] Thompson IM, Tangen CM, Goodman PJ, Lucia MS, Klein EA. Chemoprevention of prostate cancer. J Urol 2009;182:499–507.
[3] Kaye JA, Jick H. Statin use and cancer risk in the General Practice Research Database. Br J Cancer 2004;90:635–7.
[4] Paumelle R, Blanquart Ch, Briand O, et al. Acute anti-inflammatory properties of statins involve PP-AR via inhibition of the protein C signalling pathway. Circ Res 2006;98:361–9.
[5] Hayden MS, Ghosh S. Shared principles in NF kappaB signalling. Cell 2008;132:344–62.

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Re: Radical Prostatectomy Versus Watchful Waiting in Early Prostate Cancer

Bill-Axelson A, Holmberg L, Ruutu M, et al

N Engl J Med 2011;364:1708–17

Expert's summary:

This article presents long-term (median: 12.8 yr) follow-up of the Scandinavian Prostate Cancer Group 4 (SPCG-4) trial, which randomized 695 men aged $<$75 with prostate-specific antigen (PSA) $\leq$50 ng/ml and $\leq$T2N0M0 well- or moderately differentiated prostate cancer between 1989 and 1999. Progression in both arms was managed with androgen deprivation. When tumors were regraded in 1999, $>$60% were Gleason $\leq$6 and only 5% were Gleason $\geq$8. Mean age at diagnosis was 65, mean PSA was 12.9 ng/ml, and most tumors were clinically detected.

By the end of 2009, 367 (53%) of the 695 men had died, 136 (37%) from prostate cancer. The absolute and relative risk reductions for cancer-specific mortality for prostatectomy relative to watchful waiting were 6.1% and 38%, respectively. For all-cause mortality, these reductions were 6.6% and 25%, respectively, again, in favor of surgery. Subgroup analysis found that these differences were

observed even among men with low-risk disease (Gleason score <7 and PSA <10 ng/ml) but that there was no difference in outcomes between groups for men aged >65.

Expert's comments:
The results of this well-executed trial yield important insights into the evolving role of local treatment for prostate cancer. However, care should be taken in applying these findings to men diagnosed in contemporary practice. Tumors in the SPCG-4 cohort were generally clinically detected, and the lead time to clinical significance for contemporary screen-detected tumors may be even longer. Conversely, however, the cohort included few men with high-grade tumors, who may in fact be those who benefit most from surgery [1,2].

The findings of the subgroup analyses—that the benefits of surgery over watchful waiting persist across risk groups but not across age strata—are somewhat counterintuitive. In contrast, the Prostate Cancer Intervention Versus Observation Trial (PIVOT), recently reported at the American Urological Association annual meeting, randomized men between surgery and observation between 1994 and 2002. This cohort had mostly screen-detected tumors, and a survival benefit was found at 10 yr only for those with higher-risk tumors.

An analysis of older men treated conservatively for localized prostate cancer found that for those with high-grade tumors, likelihood of cancer-specific mortality approached 25% at 10 yr, even for those aged >80 at diagnosis [3], yet treatment decisions in the United States tend to reflect age more than disease risk, leading to high rates of both overtreatment of low-risk disease and undertreatment of high-risk disease among older men [4]. Other recent studies have likewise highlighted the greater role that comorbidity, rather than age alone, should play in driving both screening and management decisions [5,6]. Ultimately, the SPCG-4 trial provides important evidence in favor of intervention for localized prostate cancer, but further work is needed to identify which men will ultimately benefit most from treatment.

Conflicts of interest: The author has nothing to disclose.

References

[1] Zelefsky MJ, Eastham JA, Cronin AM, et al. Metastasis after radical prostatectomy or external beam radiotherapy for patients with clinically localized prostate cancer: a comparison of clinical cohorts adjusted for case mix. J Clin Oncol 2010;28:1508–13.
[2] Cooperberg MR, Vickers AJ, Broering JM, Carroll PR. Comparative risk-adjusted mortality outcomes after primary surgery, radiotherapy, or androgen-deprivation therapy for localized prostate cancer. Cancer 2010;116:5226–34.
[3] Lu-Yao GL, Albertsen PC, Moore DF, et al. Outcomes of localized prostate cancer following conservative management. JAMA 2009; 302:1202–9.
[4] Bechis SK, Carroll PR, Cooperberg MR. Impact of age at diagnosis on prostate cancer treatment and survival. J Clin Oncol 2011;29:235–41.
[5] Albertsen PC, Moore DF, Shih W, Lin Y, Li H, Lu-Yao GL. Impact of comorbidity on survival among men with localized prostate cancer. J Clin Oncol. In press. DOI:10.1200/JCO.2010.31.2330.
[6] Crawford ED, Grubb R, Black A, et al. Comorbidity and mortality results from a randomized prostate cancer screening trial. J Clin Oncol 2011;29:355–61.

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Re: Impact of Posterior Musculofascial Reconstruction on Early Continence After Robot-Assisted Radical Prostatectomy: Results of a Prospective Parallel Group Trial

Joshi N, de Blok W, von Muilekom E, van der Poel H

Eur Urol 2010;58:84–9

Expert's summary:
This prospective parallel group trial reported no improvement in 3-mo continence when using the "Rocco" and van Velthoven technique versus just a standard van Velthoven anastomosis. In the study group, Denonvillier's fascia was reattached to the median dorsal raphe. Some authors argue that reconstitution of these layers should improve time to continence. The present study emphasizes that those publications demonstrating a benefit from the Rocco technique all used historic controls, whereas the two studies demonstrating no improvement were prospective studies, one a randomized controlled study (RCT) and the other an alternating parallel groups study.

Expert's comments:
When designing their trial, Menon et al [1] felt they would likely find significant improvement with a double-layer repair over the standard van Velthoven technique [2] because, based on historic controls, the 1-mo continence rate (no or one pad) would be about 50%. Much to his surprise, when studied in an RCT, the van Velthoven stitch had 74% continence with no or one pad.

I first saw van Velthoven's single-knot technique in 2001, about 1 yr before I transitioned to robot-assisted radical prostatectomy (RARP). A major problem hampering the broad acceptance of laparoscopic radical prostatectomy (LRP) was the (interrupted) anastomosis. However, when van Velthoven and I collaborated with our publication in 2003, the reliability of his technique was immediately recognized, leading to broad dissemination in both LRP and RARP. The primary benefit is that the first 10 throws are evenly placed without tension. Then the sutures are cinched down, reducing and distributing the tension over the 10 needle sites. Under direct guidance, the most troublesome aspect of the anastomosis is reliably approximated. In essence, van Velthoven's stitch champions proven principles, particularly reduced tension, simplicity, and reproducibility. A multicenter survey of nine experienced centers reported a 0.8% incidence of bladder neck contractures [3].