Published in final edited form as:
*Cancer Causes Control*. 2011 November ; 22(11): 1545–1552. doi:10.1007/s10552-011-9831-7.

# Serum total and HDL cholesterol and risk of prostate cancer

**Alison M. Mondul, PhD, MSPH**[1], **Stephanie J. Weinstein, PhD**[1], **Jarmo Virtamo, MD**[2], and **Demetrius Albanes, MD**[1]

[1]Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Department of Health and Human Services, 6120 Executive Blvd. Ste. 320, Rockville, Maryland 20852 [2]Department of Chronic Disease Prevention, National Institute for Health and Welfare, P.O. Box 30, FI-00271 Helsinki, Finland

## Abstract

**Background—**Studies suggest a decreased risk of high-grade prostate cancer in men with lower circulating total cholesterol, and that statins may protect against aggressive disease. Confirmation in additional populations and examination of associations for lipoprotein subfractions are needed.

**Methods—**We examined prostate cancer risk and serum total and HDL cholesterol in the ATBC Study cohort (n=29,093). Cox proportional hazards models were used to estimate the relative risk of total (n=2,041), non –aggressive (n=829), aggressive (n=461), advanced (n=412), and high-grade (n=231) prostate cancer by categories of total and HDL cholesterol.

**Results—**After excluding the first 10 years of follow-up, men with higher serum total cholesterol were at increased risk of overall (≥240 vs. <200 mg/dL: HR=1.22, 95% CI 1.03-1.44, *p-trend=0.01*) and advanced (≥240 vs. <200 mg/dL: HR=1.85, 95% CI 1.13–3.03, *p-trend=0.05*) prostate cancer. Higher HDL cholesterol was suggestively associated with a decreased risk of prostate cancer regardless of stage or grade.

**Conclusions—**In this population of smokers, high serum total cholesterol was associated with higher risk of advanced prostate cancer, and high HDL cholesterol suggestively reduced the risk of prostate cancer overall. These results support previous studies and, indirectly, support the hypothesis that statins may reduce the risk of advanced prostate cancer by lowering cholesterol.

### Keywords

Cholesterol; HDL; Prospective Studies; Prostatic Neoplasms; Epidemiology; Risk; Molecular; Biomarker

## Introduction

Growing evidence supports the hypothesis that low cholesterol levels may protect against aggressive prostate cancer. Recent prospective studies have shown a decreased risk of high-grade prostate cancer in men with lower circulating total cholesterol [1-3]. In addition, several investigations found that statins, a class of drugs commonly prescribed to lower cholesterol, may protect against high stage or grade prostate cancer [4-10]. Earlier prospective and case-control studies examined the association between circulating cholesterol and total incident or fatal cancer and reported site-specific findings, including prostate cancer [11-24], with mixed

**Corresponding Author:** Alison Mondul 6120 Executive Blvd Ste 320 Rockville, MD 20852 Ph: (301) 496-5626 Fax: (301) 496-6829 mondulam@mail.nih.gov.

results including positive associations [22, 23], inverse associations [11, 13, 14, 20], and null associations [12, 15-19, 21, 24] reported. Most of these studies, however, included relatively few prostate cancer cases, and none reported the association for advanced or high-grade prostate cancer, although the case distribution was likely shifted toward more advanced cases in those studies conducted prior to the widespread use of PSA screening. Furthermore, the few prospective studies that examined high-density lipoprotein (HDL) cholesterol found no association [24, 25], or that higher HDL cholesterol was associated with a lower risk of prostate cancer [23, 26]. Only one of these studies examined advanced prostate cancer separately [24].

Recently, a study from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study cohort examined total and HDL cholesterol in relation to risk of cancer overall and for specific sites, including total prostate cancer [27], and found inverse associations between both total and HDL cholesterol and prostate cancer which were attenuated when the first 10 years of follow-up were excluded. Given differing etiological associations observed for overall and advanced or high-grade prostate cancer, and that the association for HDL cholesterol is understudied, we conducted a more detailed analysis of total and HDL cholesterol and risk of prostate cancer in the ATBC Study with additional years of observation.

## Methods

### Study Population

The ATBC Study, a randomized, double-blind, placebo-controlled, primary prevention trial, was conducted to determine the effects of supplementation with α-tocopherol and β-carotene on cancer incidence. A total of 29,133 Caucasian men from southwestern Finland, all of whom were smokers, were enrolled from 1985 through 1988. At baseline, men were between 50-69 years old and smoked at least 5 cigarettes per day, as part of the enrollment criteria. Men were ineligible to participate in the trial if at enrollment they had previously had cancer or another serious illness, or if they reported currently using supplements containing vitamin E (>20mg), vitamin A (>20,000 IU), or β-carotene (>6mg) on a daily basis. Men who were enrolled in the trial were randomized to one of four groups based on a 2×2 factorial design: 1) α-tocopherol (dl-α-tocopherol acetate, 50mg/day), 2) β-carotene (20 mg/day), 3) both supplements, or 4) placebo. Participants took the capsules for 5-8 years (median 6.1 years), until death, or until the trial ended on April 30, 1993.

At enrollment, participants completed questionnaires which asked about general risk factors, smoking, and medical history, and included a validated food-frequency questionnaire. Participants underwent a physical examination at baseline; registered nurses measured their height and weight and collected an overnight fasting blood sample. Fasting blood samples were collected again after 3 years on-study. Although the trial has ended, follow-up is ongoing through the Finnish Cancer Registry and the Register of Causes of Death. As of April 30, 2006, 2,041 incident prostate cancer cases occurred during 417,532 person-years of follow-up. Men were excluded from this analysis if they had missing information on baseline serum total (n=36) or HDL (n=4) cholesterol concentration, leaving 2,041 cases among 29,093 men and 417,532 person-years for baseline analyses and 1,733 cases among 22,836 men and 349,206 person-years for analyses using the 3-year follow-up measurement.

### Exposure and Outcome Assessment

Prostate cancer cases were identified by linkage with the Finnish Cancer Registry, which provides nearly 100% complete incident cancer ascertainment in Finland [28]. Medical records for the cases diagnosed prior to July 2002 were reviewed by one or two study oncologists to confirm diagnosis and staging; where available, pathologic specimens were reviewed by a pathologist. For cases diagnosed after July 2002, only the information from the Finnish

Cancer Registry is available. Cases were defined as "aggressive" if they were TNM stage III or IV, AJCC stage 3 or higher, or Gleason sum 8 or higher. Information on stage was available for 63% of the cases, and Gleason sum was available for 25% of the cases. Of the 2,041 incident cases in our study, 764 were aggressive, 412 were high stage, and 231 were high Gleason sum.

Total cholesterol was measured enzymatically (CHOD-PAP method, Boehringer Mannheim). After precipitation of very-low-density lipoprotein and low-density lipoprotein cholesterol with dextran sulfate and magnesium chloride, HDL cholesterol was measured, as well. Both total and HDL cholesterol were measured in the blood samples collected at baseline and after 3 years of follow-up. All samples were protected from light and stored at -70°C until they were assayed.

### Statistical Analysis

Cox proportional hazards modeling was used to estimate the association between clinical cutpoints of baseline serum total and HDL cholesterol and risk of total, aggressive (defined above), non-aggressive, high stage (≥ TNM stage III or AJCC stage 3), and high grade (Gleason sum ≥ 7) prostate cancer. The cholesterol exposures ere categorized based on common clinically-defined categories of <200, 200 - <240, ≥ 240 mg/dL of total cholesterol and <40, 40 - <60, ≥60 mg/dL of HDL cholesterol. We also categorized total and HDL cholesterol as quartiles and quintiles, but the inferences were similar using these cutpoints, so we present our results by clinical cutpoints. We further examined prostate cancer risk in relation to the ratio of total to HDL cholesterol (quintiles) as well as the difference in serum total and HDL cholesterol between the baseline (categories of the 3-year concentration minus baseline concentration). Men for whom information on disease stage or grade was not available were excluded from analyses of disease subtypes.

All models were adjusted for age as a continuous variable. Multivariable models were adjusted for the following factors that are hypothesized or known to be associated with either prostate cancer or total or HDL cholesterol: serum α-tocopherol, family history of prostate cancer, education level, and urban residence. Models were also each mutually adjusted for the other cholesterol type. Further adjustment for the following factors did not alter the results: α-tocopherol or β-carotene treatment group; serum β-carotene, cigarettes smoked per day, years smoked, physical activity, BMI, marital status; total energy, total fat, fruit, vegetable, red meat, alcohol, dietary retinol, vitamin D, or calcium intake; supplemental vitamin A, vitamin D, or calcium intake. Subgroup analyses were conducted stratifying by follow-up time (< 10 years, > 10 years).

## Results

Compared to men with lower baseline serum total cholesterol, men with higher cholesterol had a lower attained education level, were less likely to live in an urban area, more likely to be married, had higher serum α-tocopherol, and consumed slightly more red meat and less alcohol (Table 1). Men with higher baseline serum HDL cholesterol had a lower attained education level and were less likely to be married or live in an urban environment, had a lower BMI, lower serum α-tocopherol, and consumed more alcohol and slightly fewer fruits and vegetables than men with lower baseline serum HDL cholesterol (Table 1).

We observed no association between serum total cholesterol and risk of prostate cancer in models adjusted for age alone. With multivariable adjustment, however, there was a suggestion that men in the highest serum cholesterol category were at increased risk of overall prostate cancer, particularly high-stage disease (Table 2). The most important confounding factor in the multivariable models was baseline serum α-tocopherol, a vitamin

E molecule carried on lipoproteins; omitting serum α-tocopherol yielded results very similar to those adjusted for age alone (≥ 240 vs. < 200 mg/dL: total prostate cancer HR=1.00, 95% CI=0.88-1.12; advanced prostate cancer HR=1.06, 95% CI=0.85-1.31). Omitting HDL cholesterol from the model did not alter these findings. An inverse association between serum HDL cholesterol and risk of prostate cancer was also suggested (Table 2), and appeared similar across prostate cancer stage and Gleason sum. Omitting adjustment for total cholesterol did not alter the HDL cholesterol findings.

The increased risk of prostate cancer associated with higher serum total cholesterol was evident only in cases diagnosed at least 10 years after baseline (Table 3). This remained true after restricting to men who did not receive the trial α-tocopherol supplement (data not shown). As in the overall analysis, the positive association was accounted for by advanced prostate cancer; i.e., men with the highest serum total cholesterol were at a statistically significantly, 85% increased risk of later stage prostate cancer (*p-trend = 0.005*), compared to men with the lowest serum total cholesterol (Table 3). Even after omitting serum α-tocopherol from the model, the suggestion of a positive association with advanced prostate cancer persisted for those cases diagnosed at least 10 years after baseline (≥240 vs. <200 mg/dL: HR=1.41, 95% CI=0.91 – 2.18, *p-trend = 0.06).* These results persisted when we excluded men in the lowest and highest 1% of cholesterol values. The association for HDL cholesterol did not differ between the early and later follow-up periods (data not shown).

Examination of the total:HDL cholesterol ratio in relation to prostate cancer revealed that men in the highest quintile (i.e., those with the least desirable total:HDL cholesterol ratios from a cardiovascular perspective) were at an increased risk of total (HR=1.20, 95% CI: 1.02- 1.41) and advanced (HR=1.44, 95% CI: 1.02 – 2.05) disease compared to men in the lowest ratio quintile. We observed no association between change in serum total or HDL cholesterol between baseline and the 3-year follow-up measurement and risk of any of the prostate cancer outcomes examined (overall prostate cancer: total cholesterol increase of 10 mg/dL or more vs. no change, HR=0.94, 95% CI: 0.84 – 1.05, total cholesterol decrease of 10 mg/dL or more vs. no change, HR=0.92, 95% CI: 0.81-1.05; HDL cholesterol increase of 3 mg/dL or more vs. no change, HR=0.98, 95% CI: 0.88-1.09, HDL cholesterol decrease of 3 mg/dL or more vs. no change, HR=1.00, 95% CI: 0.88-1.13; data not shown by stage or grade). These associations remained null after excluding the first 10 years of follow-up (data not shown).

## Discussion

In this large, prospective cohort study of smokers, men with higher serum total cholesterol were at an increased risk of prostate cancer, particularly advanced stage disease, but only after excluding the first 10 years of follow-up. Men with higher HDL cholesterol appeared to have slightly lower prostate cancer risk that persisted across all categories of prostate cancer stage and grade, and throughout the follow-up period. We observed that men with higher total:HDL cholesterol ratios experienced a slightly greater increase in prostate cancer risk than men with either high total cholesterol or low HDL cholesterol alone. These results are consistent with the independent effects of total and HDL cholesterol that we observed in our main analyses.

Our findings for overall prostate cancer are slightly different from those previously reported for this cohort [27]; this difference can be attributed to our adjustment for baseline serum alpha-tocopherol, which is known to be positively associated with serum cholesterol and inversely associated with prostate cancer in this cohort. Whereas the previous analysis was an overview of the relationship between serum cholesterol and all cancer, the narrow focus of the present analysis allowed us to tailor our model and analytic strategies to prostate

cancer, in particular. The strong positive association we found here between total cholesterol and high-stage prostate cancer reinforces the etiologic importance of examining prostate cancer incidence by stage and grade, and is consistent with results from several prospective studies that found men with lower cholesterol to be at a decreased risk of aggressive prostate cancer [1-3]. These investigations found associations with high Gleason sum cancers, but were underpowered to examine advanced prostate cancer because they were conducted in the U.S. during the period of increased PSA screening. The present study was conducted in a Finnish population with little or no PSA screening and a resultant higher stage distribution at diagnosis; thus, we had greater power to examine advanced disease than did most previous analyses. Although we did not observe an association with high Gleason sum prostate cancer, our study may have been underpowered to examine that outcome because although stage information was available for a majority of the cases (63%), data for Gleason sum were available for relatively few (25%), and were primarily collected during the earlier period of the study. Thus, our results may not contradict those previously reported in the literature and, in fact, add to a growing body of literature suggesting a role for cholesterol in the etiology of high stage or grade prostate cancer. To our knowledge, our study is the first to examine the association between prediagnostic HDL cholesterol and risk of prostate cancer by stage and grade. Our results are also consistent with those from research showing reduced risk of advanced or high-grade prostate cancer among men who use statin drugs [4-10], since the latter not only lower total cholesterol, but also tend to raise HDL cholesterol [29].

Our results differ from those of previous studies in that we only observed an association between serum cholesterol and risk of prostate cancer in cases that were diagnosed more than 10 years after baseline. One possible explanation for this finding is reverse causation during the earlier follow-up period. If men with undiagnosed prostate cancer at baseline have low cholesterol as a result of their cancer, cases diagnosed early in follow-up are likely to be overrepresented in the referent group, making the association with high cholesterol appear null during the earlier follow-up period. Other recent studies have not observed reverse causation [1-3], but two of these studies were conducted in highly screened populations [1, 2], as opposed to the current study population where PSA screening continues to be uncommon. Reverse causation is more likely in an unscreened population because cholesterol levels are likely to be more affected by cancer that is further along in the disease's natural history and it is less likely that advanced cases would be undiagnosed at the time of blood collection in a highly screened population. Although the interaction with follow-up time could theoretically be explained by a protective effect of the trial α-tocopherol supplement during the earlier follow-up period, this explanation is not supported by the persistence of the association among men who did not receive the trial vitamin E supplement.

Several mechanisms have been hypothesized through which total cholesterol may increase prostate cancer risk. Prostate cancer cells tend to over-accumulate cholesterol in their cell membranes, forming large lipid rafts which, in the case of cancer cells, may facilitate pro-carcinogenic cell signaling [30]. Further, several pathways that are important in carcinogenesis, such as the sonic hedgehog and Akt pathways, are cholesterol sensitive [30]. Thus, having lower cholesterol may inhibit their pro-carcinogenic activities. One of the important functions of HDL cholesterol, the transport of cholesterol from cells to the liver and other steroidogenic organs [31], is thought to be the mechanism through which HDL protects against atherosclerotic cardiovascular disease, and may also remove harmful cholesterol from prostate tissue, thereby protecting against prostate cancer via the mechanisms discussed above. In addition, HDL inhibits oxidation and inflammation, properties which may also reduce prostate cancer risk [31]. On the other hand, a recent study showed that HDL cholesterol induced the proliferation of androgen-independent prostate

cancer cells [32], suggesting that the relation between HDL cholesterol and prostate cancer may be complex.

One alternative explanation for our findings is detection bias: i.e., men with higher total cholesterol levels are less health conscious and are, therefore, less likely to undergo screening that would detect prostate cancer at an earlier stage, increasing their risk of being detected at a more advanced stage. This seems unlikely given that the prevalence of PSA screening was quite low in this population, even in the later follow-up period, as mentioned. Studies have estimated that as of 1999 (i.e. during our latter follow-up period) <20% of men in Finland were receiving PSA screening [33]. Detection bias could still have occurred through digital rectal examinations (DRE) by physicians. However, given the similar results observed here and in prior studies of PSA-screened U.S. populations, detection bias is an unlikely explanation for the associations.

Our study is the largest to date to examine serum total cholesterol, and one of the few to examine HDL cholesterol, in relation to risk of prostate cancer by clinical characteristics. The emerging consistency of findings across various populations supports the overall hypothesis that cholesterol status influences prostate carcinogenesis. Strengths of our study include the complete population-based case ascertainment, information and measurements for many potential confounders, assessment of serum total and HDL cholesterol for the entire cohort at two points in time 3 years apart, and uniform assays in one dedicated laboratory. We were unable to evaluate nonsmokers, however, or directly assess whether LDL cholesterol or cholesterol lowering from high to desirable levels reduces the incidence of advanced stage prostate cancer. We were also unable to adjust for potential confounding variables as time-dependent variables.

## Conclusion

In this population of male smokers with a low prevalence of PSA screening, high serum total cholesterol was associated with an increased risk of advanced prostate cancer, and there was a suggestion that high HDL cholesterol reduced the risk of prostate cancer overall. These findings support those from previous studies and, indirectly, are consistent with the hypothesis that statin drugs reduce the risk of high stage or grade prostate cancer through their cholesterol-lowering effects.

## Acknowledgments

**Funding:** This work was supported by U.S. Public Health Service contracts from the National Cancer Institute, Department of Health and Human Services (N01-CN-45165, N01-RC-45035, N01-RC-37004, and HHSN261201000006C); and by funding from the Intramural Research Program of the National Cancer Institute.

## References

1. Platz EA, Clinton SK, Giovannucci E. Association between plasma cholesterol and prostate cancer in the PSA era. International journal of cancer. Journal international du cancer. 2008; 123(7):1693–98. [PubMed: 18646186]
2. Platz EA, Till C, Goodman PJ, et al. Men with low serum cholesterol have a lower risk of high grade prostate cancer in the Prostate Cancer Prevention Trial. Cancer epidemiology, biomarkers & prevention. 2009 in press.
3. Mondul AM, Clipp SL, Helzlsouer KJ, Platz EA. Association between plasma total cholesterol concentration and incident prostate cancer in the CLUE II cohort. Cancer Causes Control. 21(1):61–8. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19806465. [PubMed: 19806465]

4. Shannon J, Tewoderos S, Garzotto M, et al. Statins and prostate cancer risk: a case-control study. American Journal of Epidemiology. 2005; 162(4):318–25. [PubMed: 16014776]
5. Platz EA, Leitzmann MF, Visvanathan K, et al. Statin Drugs and Risk of Advanced Prostate Cancer. Journal of the National Cancer Institute. 2006; 98(24):1819–25. [PubMed: 17179483]
6. Jacobs EJ, Rodriguez C, Bain EB, Wang Y, Thun MJ, Calle EE. Cholesterol-lowering drugs and advanced prostate cancer incidence in a large U.S. cohort. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2007; 16(11):2213–17.
7. Murtola TJ, Tammela TL, Lahtela J, Auvinen A. Cholesterol-lowering drugs and prostate cancer risk: a population-based case-control study. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2007; 16(11):2226–32.
8. Flick ED, Habel LA, Chan KA, et al. Statin use and risk of prostate cancer in the California Men's Health Study cohort. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2007; 16(11):2218–25.
9. Agalliu I, Salinas CA, Hansten PD, Ostrander EA, Stanford JL. Statin use and risk of prostate cancer: results from a population-based epidemiologic study. American Journal of Epidemiology. 2008; 168(3):250–60. [PubMed: 18556686]
10. Friedman GD, Flick ED, Udaltsova N, Chan Pharm DJ, Quesenberry CP Jr. Habel LA. Screening statins for possible carcinogenic risk: up to 9 years of follow-up of 361 859 recipients. Pharmacoepidemiology and drug safety. 2008; 17(1):27–36. [PubMed: 17944002]
11. Kark JD, Smith AH, Hames CG. Serum retinol and the inverse relationship between serum cholesterol and cancer. British medical journal (Clinical research ed.). 1982; 284(6310):152–54. [PubMed: 6799076]
12. Wallace RB, Rost C, Burmeister LF, Pomrehn PR. Cancer incidence in humans: relationship to plasma lipids and relative weight. Journal of the National Cancer Institute. 1982; 68(6):915–18. [PubMed: 6953272]
13. Hiatt RA, Fireman BH. Serum cholesterol and the incidence of cancer in a large cohort. Journal of chronic diseases; Journal of chronic diseases. 1986; 39(11):861–70.
14. Knekt P, Reunanen A, Aromaa A, Heliovaara M, Hakulinen T, Hakama M. Serum cholesterol and risk of cancer in a cohort of 39,000 men and women. Journal of clinical epidemiology. 1988; 41(6):519–30. [PubMed: 3290396]
15. Thompson MM, Garland C, Barrett-Connor E, Khaw KT, Friedlander NJ, Wingard DL. Heart disease risk factors, diabetes, and prostatic cancer in an adult community. American Journal of Epidemiology. 1989; 129(3):511–17. [PubMed: 2916544]
16. Chyou PH, Nomura AM, Stemmermann GN, Kato I. Prospective study of serum cholesterol and site-specific cancers. Journal of clinical epidemiology. 1992; 45(3):287–92. [PubMed: 1569426]
17. Smith GD, Shipley MJ, Marmot MG, Rose G. Plasma cholesterol concentration and mortality. The Whitehall Study. JAMA : the journal of the American Medical Association. 1992; 267(1):70–76. [PubMed: 1727199]
18. Schuit AJ, Van Dijk CE, Dekker JM, Schouten EG, Kok FJ. Inverse association between serum total cholesterol and cancer mortality in Dutch civil servants. American Journal of Epidemiology. 1993; 137(9):966–76. [PubMed: 8317454]
19. Steenland K, Nowlin S, Palu S. Cancer incidence in the National Health and Nutrition Survey I. Follow-up data: diabetes, cholesterol, pulse and physical activity. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology; Cancer epidemiology, biomarkers & prevention : a publication of the America(TRUNCATED). 1995; 4(8):807–11.
20. Eichholzer M, Stahelin HB, Gutzwiller F, Ludin E, Bernasconi F. Association of low plasma cholesterol with mortality for cancer at various sites in men: 17-y follow-up of the prospective Basel study. The American Journal of Clinical Nutrition. 2000; 71(2):569–74. [PubMed: 10648273]

21. Wuermli L, Joerger M, Henz S, et al. Hypertriglyceridemia as a possible risk factor for prostate cancer. Prostate cancer and prostatic diseases. 2005; 8(4):316–20. [PubMed: 16158078]
22. Bravi F, Scotti L, Bosetti C, et al. Self-reported history of hypercholesterolaemia and gallstones and the risk of prostate cancer. Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO; Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO. 2006; 17(6):1014–17.
23. Magura L, Blanchard R, Hope B, Beal JR, Schwartz GG, Sahmoun AE. Hypercholesterolemia and prostate cancer: a hospital-based case-control study. Cancer Causes Control. 2008; 19(10):1259–66. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18704722. [PubMed: 18704722]
24. Martin RM, Vatten L, Gunnell D, Romundstad P, Nilsen TI. Components of the metabolic syndrome and risk of prostate cancer: the HUNT 2 cohort, Norway. Cancer Causes Control. 2009; 20(7):1181–92. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19277881. [PubMed: 19277881]
25. Tuohimaa P, Tenkanen L, Syvala H, et al. Interaction of factors related to the metabolic syndrome and vitamin D on risk of prostate cancer. Cancer Epidemiol Biomarkers Prev. 2007; 16(2):302–7. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17301263. [PubMed: 17301263]
26. Van Hemelrijck M, Walldius G, Jungner I, et al. Low levels of apolipoprotein A-I and HDL are associated with risk of prostate cancer in the Swedish AMORIS study. Cancer Causes Control. 22(7):1011–9. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21562751. [PubMed: 21562751]
27. Ahn J, Lim U, Weinstein SJ, et al. Prediagnostic total and high-density lipoprotein cholesterol and risk of cancer. Cancer Epidemiol Biomarkers Prev. 2009; 18(11):2814–21. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19887581. [PubMed: 19887581]
28. Korhonen P, Malila N, Pukkala E, Teppo L, Albanes D, Virtamo J. The Finnish Cancer Registry as follow-up source of a large trial cohort--accuracy and delay. Acta Oncol. 2002; 41(4):381–8. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12234031. [PubMed: 12234031]
29. Edwards JE, Moore RA. Statins in hypercholesterolaemia: a dose-specific meta-analysis of lipid changes in randomised, double blind trials. BMC family practice. 2003; 4:18. [PubMed: 14969594]
30. Solomon KR, Freeman MR. Do the cholesterol-lowering properties of statins affect cancer risk? Trends in endocrinology and metabolism: TEM. 2008; 19(4):113–21. [PubMed: 18356074]
31. Kwiterovich PO Jr. The metabolic pathways of high-density lipoprotein, low-density lipoprotein, and triglycerides: a current review. Am J Cardiol. 2000; 86(12A):5L–10L. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11374859.
32. Sekine Y, Demosky SJ, Stonik JA, et al. High-density lipoprotein induces proliferation and migration of human prostate androgen-independent cancer cells by an ABCA1-dependent mechanism. Mol Cancer Res. 8(9):1284–94. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20671065. [PubMed: 20671065]
33. Ciatto S, Zappa M, Villers A, Paez A, Otto SJ, Auvinen A. Contamination by opportunistic screening in the European Randomized Study of Prostate Cancer Screening. BJU Int. 2003; 92(Suppl 2):97–100. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14983964. [PubMed: 14983964]

**Table 1**

Age-adjusted[a] baseline[b] characteristics by baseline serum total and HDL cholesterol, ATBC Study, 1985 – 2006

| | Total Cholesterol (mg/dL) | | | HDL Cholesterol (mg/dL) | | |
|---|---|---|---|---|---|---|
| | **< 200** | **200 - <240** | **≥ 240** | **< 40** | **40 - < 60** | **≥ 60** |
| **N (%)** | 4,979 (17.1) | 10,092 (34.7) | 14,022 (48.2) | 9,998 (34.4) | 15,316 (52.6) | 3,779 (13.0) |
| **Age** | 57.6 | 57.2 | 57.1 | 57.2 | 57.2 | 57.1 |
| **BMI (kg/m$^2$)** | 26.1 | 26.2 | 26.4 | 27.6 | 25.9 | 24.1 |
| **Serum α-tocopherol (mg/L)** | 9.17 | 11.0 | 13.6 | 12.8 | 11.6 | 10.9 |
| **Cigarettes/day** | 20.7 | 20.3 | 20.4 | 20.5 | 20.3 | 20.9 |
| **Years of smoking** | 35.9 | 35.9 | 36.0 | 36.1 | 35.8 | 36.1 |
| **Family history of prostate cancer** | | | | | | |
| n (%) | 105 (3.5) | 211 (3.3) | 302 (3.3) | 209 (3.3) | 348 (3.5) | 61 (2.7) |
| **Physically active** | | | | | | |
| n (%) | 960 (19.8) | 2,137 (21.2) | 2,945 (20.8) | 1,960 (19.6) | 3,324 (21.8) | 758 (19.9) |
| **Education (> Elementary)** | | | | | | |
| n (%) | 1,143 (23.0) | 2,173 (21.5) | 2,800 (20.0) | 2,227 (22.2) | 3,167 (20.7) | 722 (19.1) |
| **Married** | | | | | | |
| n (%) | 3,749 (76.2) | 8,076 (80.0) | 11,462 (81.7) | 8,216 (82.2) | 12,340 (80.6) | 2,776 (73.5) |
| **Urban residence** | | | | | | |
| n (%) | 3,052 (61.3) | 5,976 (59.2) | 8,160 (58.2) | 6,020 (60.2) | 8,978 (58.6) | 2,190 (57.9) |
| **Intake (daily)** | | | | | | |
| **Total energy (kcal)** | 2,689 | 2,690 | 2,687 | 2,662 | 2,707 | 2,690 |
| **Total fat (g)** | 99.6 | 100.7 | 101.7 | 100.0 | 102.0 | 99.3 |
| **Fruit (g/day)** | 219.5 | 217.9 | 217.5 | 232.5 | 212.2 | 202.6 |
| **Vegetables (g)** | 291.8 | 292.7 | 294.0 | 295.1 | 293.5 | 286.2 |
| **Red meat (g)** | 69.4 | 70.6 | 72.4 | 71.2 | 71.2 | 71.8 |
| **Alcohol (g)** | 18.8 | 18.2 | 17.5 | 13.6 | 18.5 | 27.8 |

[a]Directly-standardized to the age distribution of the entire cohort. Values are mean values unless otherwise indicated.

[b]All characteristics are from the baseline questionnaire except family history which was collected during follow-up and is available for 18,750 men.

*Cancer Causes Control*. Author manuscript; available in PMC 2012 November 19.

**Table 2**

Cox proportional hazards models of serum total and HDL cholesterol and risk of prostate cancer, ATBC Study, 1985 – 2006

| | Total Cholesterol (mg/dL) | | | | HDL Cholesterol (mg/dL) | | | |
|---|---|---|---|---|---|---|---|---|
| | **<200** | **200 - <240** | **≥240** | ***p-trend*** | **<40** | **40 - <60** | **≥ 60** | ***p-trend*** |
| **All Prostate Cancer** | | | | | | | | |
| # cases | 348 | 669 | 1,024 | | 713 | 1,084 | 244 | |
| HR (95% CI)[a] | 1.0 (ref) | 0.90 (0.79 – 1.02) | 0.98 (0.87 – 1.11) | *0.63* | 1.0 (ref) | 0.95 (0.86 – 1.04) | 0.93 (0.80 – 1.07) | *0.23* |
| HR (95% CI)[b] | 1.0 (ref) | 0.96 (0.84 – 1.10) | 1.14 (0.99 – 1.31) | *0.01* | 1.0 (ref) | 0.92 (0.83 – 1.01) | 0.89 (0.77 – 1.03) | *0.07* |
| **Non-Aggressive Prostate Cancer** | | | | | | | | |
| # cases | 146 | 285 | 398 | | 299 | 433 | 97 | |
| HR (95% CI)[a] | 1.0 (ref) | 0.93 (0.76 – 1.13) | 0.93 (0.77 – 1.12) | *0.55* | 1.0 (ref) | 0.90 (0.78 – 1.04) | 0.87 (0.69 – 1.09) | *0.14* |
| HR (95% CI)[b] | 1.0 (ref) | 0.99 (0.81 – 1.21) | 1.07 (0.86 – 1.33) | *0.45* | 1.0 (ref) | 0.88 (0.76 – 1.02) | 0.85 (0.67 – 1.07) | *0.09* |
| **Aggressive Prostate Cancer** | | | | | | | | |
| # cases | 81 | 149 | 231 | | 151 | 257 | 53 | |
| HR (95% CI)[a] | 1.0 (ref) | 0.88 (0.67 – 1.15) | 0.99 (0.77 – 1.28) | *0.69* | 1.0 (ref) | 1.06 (0.87 – 1.30) | 0.94 (0.69 – 1.28) | *0.87* |
| HR (95% CI)[b] | 1.0 (ref) | 0.96 (0.73 – 1.27) | 1.20 (0.89 – 1.61) | *0.10* | 1.0 (ref) | 1.02 (0.83 – 1.25) | 0.89 (0.65 – 1.22) | *0.58* |
| **Stage ≥3** | | | | | | | | |
| # cases | 74 | 122 | 216 | | 136 | 230 | 46 | |
| HR (95% CI)[a] | 1.0 (ref) | 0.78 (0.59 – 1.05) | 1.00 (0.77 – 1.30) | *0.33* | 1.0 (ref) | 1.06 (0.86 – 1.31) | 0.90 (0.65 – 1.26) | *0.73* |
| HR (95% CI)[b] | 1.0 (ref) | 0.87 (0.65 – 1.17) | 1.26 (0.92 – 1.71) | *0.03* | 1.0 (ref) | 0.87 (0.65 – 1.17) | 0.85 (0.60 – 1.19) | *0.44* |
| **Gleason Sum ≥7** | | | | | | | | |
| # cases | 32 | 91 | 108 | | 85 | 117 | 29 | |
| HR (95% CI)[a] | 1.0 (ref) | 1.36 (0.91 – 2.03) | 1.17 (0.79 – 1.74) | *0.85* | 1.0 (ref) | 0.86 (0.65 – 1.14) | 0.91 (0.60 – 1.39) | *0.48* |
| HR (95% CI)[b] | 1.0 (ref) | 1.39 (0.92 – 2.09) | 1.20 (0.77 – 1.86) | *0.80* | 1.0 (ref) | 0.86 (0.65 – 1.15) | 0.90 (0.59 – 1.39) | *0.49* |

[a] Adjusted for age (continuous).

[b] Adjusted for age (continuous), serum α-tocopherol, family history of prostate cancer, education, urban residence. Models of serum total and HDL cholesterol are mutually adjusted for each other.

**Table 3**

Cox proportional hazards models of serum total cholesterol and risk of prostate cancer stratified by follow-up time, ATBC Study, 1985 – 2006

| | <10 years follow-up | | | ≥ 10 years follow-up | | |
|---|---|---|---|---|---|---|
| **Total Cholesterol (mg/dL)** | **<200** | **200 - <240** | **≥240** | **<200** | **200 - <240** | **≥240** |
| **All Prostate Cancer** | | | | | | |
| # cases | 129 | 183 | 300 | 219 | 486 | 724 |
| HR (95% CI)[a] | 1.0 (ref) | 0.75 (0.60 – 0.95) | 0.95 (0.75 – 1.21) | 1.0 (ref) | 1.07 (0.91 – 1.26) | 1.22 (1.03 – 1.44) |
| | | *p trend = 0.66* | | | *p trend =0.01* | |
| **Non-Aggressive Prostate Cancer** | | | | | | |
| # cases | 78 | 107 | 177 | 68 | 178 | 221 |
| HR (95% CI)[a] | 1.0 (ref) | 0.72 (0.54 – 0.98) | 0.94 (0.69 – 1.28) | 1.0 (ref) | 1.28 (0.96 – 1.70) | 1.21 (0.89 – 1.64) |
| | | *p trend = 0.75* | | | *p trend = 0.46* | |
| **Aggressive Prostate Cancer** | | | | | | |
| # cases | 51 | 74 | 120 | 30 | 75 | 111 |
| HR (95% CI)[a] | 1.0 (ref) | 0.75 (0.52 – 1.09) | 0.94 (0.64 – 1.37) | 1.0 (ref) | 1.32 (0.85 – 2.03) | 1.64 (1.04 – 2.60) |
| | | *p trend =0.86* | | | *p trend =0.03* | |
| **Stage ≥3** | | | | | | |
| # cases | 49 | 64 | 113 | 25 | 58 | 103 |
| HR (95% CI)[a] | 1.0 (ref) | 0.69 (0.47 – 1.00) | 0.94 (0.64 – 1.39) | 1.0 (ref) | 1.23 (0.76 – 1.98) | 1.85 (1.13 – 3.03) |
| | | *p trend =0.71* | | | *p trend =0.005* | |
| **Gleason Sum ≥7** | | | | | | |
| # cases | 17 | 34 | 47 | 15 | 57 | 61 |
| HR (95% CI)[a] | 1.0 (ref) | 1.03 (0.57 – 1.87) | 1.05 (0.57 – 1.94) | 1.0 (ref) | 1.75 (0.98 – 3.11) | 1.32 (0.72 – 2.45) |
| | | *p trend =0.89* | | | *p trend =0.94* | |

[a]Adjusted for age (continuous), serum α-tocopherol, family history of prostate cancer, education, and urban residence.