

Research Article

Obesity Increases the Risk for High-Grade Prostate Cancer: Results from the REDUCE StudyAdriana C. Vidal^{1,2}, Lauren E. Howard^{2,3}, Daniel M. Moreira⁴, Ramiro Castro-Santamaria⁵, Gerald L. Andriole Jr⁶, and Stephen J. Freedland^{2,3,7}**Abstract**

Background: Studies suggest that obesity is associated with lower risk of prostate cancer but more aggressive cancers. As obesity lowers PSA levels, these observations may be influenced by detection bias. We examined the association between obesity and risk of low- and high-grade prostate cancer in REDUCE, in which biopsies were largely independent of PSA.

Methods: The REDUCE study tested dutasteride for prostate cancer risk reduction in men with a PSA of 2.5 to 10.0 ng/mL and a negative biopsy. Study participants included 6,729 men who underwent at least one on-study biopsy. The association between baseline body mass index (BMI <25 kg/m² normal weight; 25–29.9 kg/m² overweight; and ≥30 kg/m² obese) and risk of high-grade (Gleason ≥7) or low-grade prostate cancer (Gleason <7) versus no prostate cancer was examined using multinomial logistic regression.

Results: Overall, 1,739 men (27%) were normal weight, 3,384 (53%) overweight, and 1,304 (20%) were obese. Obesity was associated with lower risk of low-grade prostate cancer in both univariable (OR, 0.74; *P* = 0.001) and multivariable analyses (OR, 0.79; *P* = 0.01). In univariable analysis, obesity was not associated with high-grade prostate cancer (OR, 1.08; *P* = 0.50). However, in multivariable analysis, obesity was associated with increased risk of high-grade prostate cancer (OR, 1.28; *P* = 0.042). This analysis was not able to address how obesity may influence prostate cancer progression.

Conclusions: Obesity is associated with decreased risk of low-grade and increased risk of high-grade prostate cancer. These data provide further support to the hypothesis that obesity is associated with aggressive prostate cancer.

Impact: Obesity is linked with aggressive prostate cancer. Avoiding obesity may prevent the risk of developing high-grade prostate cancer. *Cancer Epidemiol Biomarkers Prev*; 23(12); 2936–42. ©2014 AACR.

Introduction

Obesity is a global epidemic. Though obesity is an established risk factor for many cancers, the association is not clear with total prostate cancer risk (1,2), the most common nonskin cancer among men and the sixth most common cause of cancer-related death among men globally (3).

A recent meta-analysis of prospective cohort studies, including more than 2,000,000 men worldwide, found that obese men are at increased risk of advanced prostate cancer, but lower risk of localized prostate cancer (4). Multiple reasons for this association have been postulated (1). One possibility is that obese men have lower PSA levels (5–7). Given only men with abnormal PSAs are typically referred for biopsy, if obesity lowers PSA, this could lead to fewer biopsies and reduced cancer detection. The missed cancers in obese men would continue to grow and be detected at a later more aggressive stage. Thus, detection bias could explain the observed association between obesity and increased risk of high-grade prostate cancer and decreased risk of low-grade prostate cancer.

Alternatively, obesity may biologically be linked with fewer nonaggressive cancers and yet more aggressive cancers. Indeed, a prior randomized trial of finasteride versus placebo for prostate cancer prevention showed that among men who underwent end-of-study biopsy, obesity was associated with lower risk of low-grade prostate cancer but increased risk of high-grade

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doi: 10.1158/1055-9965.EPI-14-0795

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prostate cancer (8). However, in that study, nearly 40% of men refused biopsy (8). Although the reasons for refusing biopsy were not reported, it is conceivable that men with lower PSA values elected not to undergo biopsy. Thus, although these data support the suggestion that obesity may be linked with fewer low-grade but more high-grade prostate cancer on a biologic level, to what degree these results were free of PSA bias is unclear.

To test the association between obesity and prostate cancer risk independent of PSA, we examined this association in the REDUCE study, a 4-year randomized trial of dutasteride versus placebo on prostate cancer risk (9). Importantly, the REDUCE study mandated biopsies at 2 and 4 years regardless of PSA. Given that nearly 83% of men had at least one biopsy performed and >93% were per-protocol (i.e., performed regardless of PSA), this study provides a unique opportunity to test the association between obesity and prostate cancer risk largely independent of PSA. We hypothesized that obesity would predict lower risk of low-grade but higher risk of high-grade prostate cancer risk after controlling for clinical covariates.

Materials and Methods

Study population

The design of the REDUCE study has been reported previously (9). Eligible men were of ages 50 to 75 years, with a serum PSA of 2.5 to 10 ng/mL if ages 50 to 60 years, or 3 to 10 ng/mL if >60 years, and a single, negative prostate biopsy (6–12 cores) within 6 months before enrollment (independent of the study).

Study design. REDUCE was a 4-year, multicenter, double-blind, placebo-controlled study (9). Eligible subjects were randomized to dutasteride 0.5 mg/d or placebo. Visits occurred every 6 months. Total serum PSA (Beckman Coulter Inc.) was assessed every 6 months, with doubled PSA values (± 0.1 ng/mL in half of the subjects) reported to investigators for men receiving dutasteride (9). Unscheduled PSA measurements were permitted if obtained through the central study laboratory.

Subjects underwent 10-core transrectal ultrasound (TRUS)-guided biopsy at 2 and 4 years regardless of PSA levels ("protocol-dependent" biopsies); unscheduled biopsies were performed if clinically indicated ("protocol-independent" biopsies). For-cause biopsies obtained during months 19 to 24 and 43 to 48 replaced those scheduled for years 2 and 4, and were included in the definition of protocol-dependent biopsies.

At baseline, a detailed medical history was obtained, including smoking history, alcohol use, medication use, and medical comorbidities. Height and weight were measured and body mass index (BMI; kg/m^2) was calculated. Race was self-reported. Digital rectal examination (DRE) findings and TRUS prostate volume were reported from the pre-study biopsy.

Statistical analysis

Among 8,122 men included in the efficacy population, we limited analyses to 6,729 (82.8%) who underwent at least one biopsy. There were no differences in BMI between men who did and did not undergo at least one on-study biopsy (rank-sum, $P = 0.15$). Moreover, men who did not undergo a biopsy were of similar age, and had similar baseline PSA values, and DRE findings (all $P > 0.05$). There were significant racial differences between men who did and did not undergo a biopsy ($P < 0.001$). Specifically, black men were overrepresented among men who did not receive a biopsy versus the whole study population (3.9 vs. 1.9%). Further details of the biopsy population have been previously published (10). Moreover, obese men were equally likely to receive a second biopsy when compared with nonobese men ($P > 0.24$).

Among 6,729 men with at least one on-study biopsy, we excluded men with missing data for BMI ($n = 205$), PSA ($n = 14$), DRE ($n = 7$), or TRUS volume ($n = 76$) resulting in a study population of 6,427.

BMI was initially characterized as normal weight ($< 25 \text{ kg}/\text{m}^2$), overweight ($25\text{--}29.9 \text{ kg}/\text{m}^2$), and obese ($\geq 30 \text{ kg}/\text{m}^2$). Men with BMI < 18.5 were not excluded ($n = 22$). The association between BMI and baseline parameters was tested using Kruskal–Wallis for continuous variables and χ^2 for categorical variables. The association between BMI and PSA as a continuous variable was further explored to determine the mean-adjusted PSA stratified by BMI category. This was done using linear regression controlling for age (continuous), race (white, black, and other), prostate volume (continuous and log transformed), and DRE findings (suspicious for cancer vs. not). To determine which factor accounted for the differences between the univariable result and the multivariate result, each potential confounding variable was added to the univariable model one at a time.

The OR associated with BMI category at baseline and risk of high-grade (Gleason ≥ 7) or low-grade prostate cancer (Gleason < 7) relative to no cancer was examined using multinomial logistic regression. Crude analyses were unadjusted. Multivariable results were adjusted for clinical characteristics known to be associated with prostate cancer risk, including age, race, baseline PSA, prostate volume, DRE findings, BMI, and treatment arm (dutasteride vs. placebo), using the same variable definitions as in the univariable results. Further adjustment for smoking, alcohol, diabetes, coronary artery disease, hypertension, and testosterone and DHT levels did not materially affect the results and thus were not included in the final model. Given results for overweight and normal weight men were similar, BMI was then categorized as obese ($\geq 30 \text{ kg}/\text{m}^2$) versus nonobese ($< 30 \text{ kg}/\text{m}^2$). We examined whether the association between obesity and cancer risk differed by age ($<$ vs. $>$ median), TRUS volume ($<$ vs. $>$ median), smoking status, hypertension, serum androgen levels ($<$ vs. $>$ median), and treatment arm (dutasteride vs. placebo) using stratified analysis and by testing for

interactions by including a cross product term along with both main effect terms in the multivariable model. These analyses were adjusted for PSA, age, race, TRUS volume, treatment arm, and DRE findings. There were not enough non-White men, men with a suspicious DRE, or men with diabetes or coronary artery disease to test for interactions and thus such analyses were not done. All analyses were conducted using Stata 10.1 and a *P* value of <0.05 was set as the threshold for statistical significance.

Results

Study population and baseline characteristics

Overall, 1,739 men (27%) were normal weight, 3,384 (53%) overweight, and 1,304 (20%) were obese. Higher BMI was associated with a lower PSA (*P* = 0.06), but also larger prostate volume (*P* = 0.0001) and younger age (*P* = 0.0001), though the association with PSA was not significant. Overweight and obese men had more total number of cores taken on the baseline biopsy compared with normal weight men (*P* = 0.012). The percentage of men who had an off-study biopsy was similar among the three groups (*P* = 0.717). Though race was significantly associated with BMI (*P* = 0.002), the overall differences were slight (Table 1). After adjusting for age, prostate volume, and racial differences among the BMI groups, both overweight (*P* = 0.003), and obese men (*P* = 0.013) had significantly lower PSA values than normal weight men (data not shown).

Obesity, cancer risk, and tumor volume

Prostate cancer was detected in 1,448 men (23%), which was low-grade in 1,008 (16%), and high-grade in 440 (7%).

In crude unadjusted analyses, obesity was associated with overall decreased prostate cancer risk [OR, 0.84; 95% confidence interval (CI), 0.72–0.98; *P* = 0.02], a lower risk of low-grade disease (OR, 0.74; 95% CI, 0.62–0.89; *P* = 0.001) and was unrelated to high-grade disease (OR, 1.08; 95% CI, 0.86–1.37; *P* = 0.50). After adjusting for multiple clinical features and treatment arm, obesity was not associated with overall prostate cancer risk (OR, 0.92; 95% CI, 0.79–1.07; *P* = 0.28), although it was statistically significantly related to a lower risk of low-grade disease (OR, 0.79; 95% CI, 0.65–0.94; *P* = 0.01) and higher risk of high-grade disease (OR, 1.28; 95% CI, 1.01–1.63; *P* = 0.04; Table 2). To determine which factor accounted for the differences between the univariable and multivariable result, each potential confounding variable was added to the univariable model one at a time. Age and TRUS volume resulted in the greatest change in the OR for obesity and high-grade but not low-grade disease, suggesting in this cohort, these two variables were the greatest confounders. Further adjusting for serum hormonal levels (testosterone and DHT), lifestyle factors (smoking and alcohol use), or comorbidities (coronary artery disease, hypertension, or diabetes), did not materially change the magnitude nor the direction of the associations.

When stratified by treatment arm, the association between obesity and lower risk of low grade and higher risk of high grade was more pronounced for men assigned to dutasteride (Table 2). However, the interaction between treatment arm and obesity was not significant (all *P*_{interactions} ≥ 0.40).

Among men with cancer, tumor volume on biopsy was known for 1,444 (99%). Among these men, though the direction of the association was for obese men to have

Table 1. Clinical characteristics of men in the REDUCE trial who had at least one on-study biopsy stratified by obesity status

	Normal weight <25 kg/m ²	Overweight 25–29.9 kg/m ²	Obese ≥30 kg/m ²	<i>P</i> ^a
Number of patients (%)	1,739 (27)	3,384 (53)	1,304 (20)	
Age, median (IQR; y)	64 (59–68)	63 (58–67)	62 (57–66)	0.0001
PSA, median (IQR), ng/mL	5.8 (4.5–7.4)	5.7 (4.4–7.3)	5.7 (4.3–7.3)	0.06
Race, <i>n</i> (%)				0.002†
White	1,561 (90)	3,136 (93)	1,197 (92)	
Black	33 (2)	56 (2)	30 (2)	
Other	145 (8)	192 (6)	77 (6)	
DRE findings, <i>n</i> (%)				0.58†
Not suspicious	1,669 (96)	3,265 (96)	1,252 (96)	
Suspicious for cancer	70 (4)	119 (4)	52 (4)	
TRUS volume, median (IQR), cc	41 (32–54)	44 (33–57)	46 (35–59)	0.0001
Total cores on baseline biopsy (IQR)	8 (6–10)	9 (6–10)	10 (6–10)	0.012
2-year biopsy type, <i>n</i> (%)				0.717†
Protocol-mandated	1,565 (90)	3,059 (90)	1,185 (91)	
Off-study	174 (10)	325 (10)	119 (9)	

^a*P* value assessed by the Kruskal–Wallis test unless otherwise specified.

Table 2. ORs for the association between obesity and risk of overall, low-grade, and high-grade prostate cancer in the REDUCE study

	Overall cancer ^b			Low-grade cancer ^b Gleason (≤ 6)			High-grade cancer ^b Gleason (≥ 7)		
	Cases	OR ^a (95% CI)	P	Cases	OR ^a (95% CI)	P	Cases	OR ^a (95% CI)	P
All men (N = 6,427)									
Crude analysis	1,448 (23%)	0.84 (0.72–0.98)	0.022	1,008 (16%)	0.74 (0.62–0.89)	0.001	440 (7%)	1.08 (0.86–1.37)	0.50
Adjusted analysis ^a		0.92 (0.79–1.07)	0.28		0.79 (0.65–0.94)	0.01		1.28 (1.01–1.63)	0.04
Placebo arm (N = 3,270)									
Crude analysis	823 (25%)	0.84 (0.69–1.03)	0.10	594 (18%)	0.79 (0.62–0.99)	0.04	229 (7%)	0.99 (0.71–1.39)	0.98
Adjusted analysis ^a		0.92 (0.75–1.13)	0.45		0.84 (0.66–1.06)	0.15		1.18 (0.84–1.66)	0.35
Dutasteride arm (N = 3,157)									
Crude analysis	635 (20%)	0.83 (0.66–1.04)	0.11	414 (13%)	0.67 (0.50–0.89)	0.006	221 (7%)	1.18 (0.85–1.65)	0.32
Adjusted analysis ^a		0.91 (0.73–1.15)	0.44		0.71 (0.53–0.95)	0.02		1.41 (1.00–1.98)	0.05

^aAdjusted for age, race, PSA, DRE findings, TRUS volume, and study treatment arm.

^bReferents were nonobese men (BMI <30 kg/m²) and no cancer.

larger tumors, these results were not statistically significant ($P = 0.12$; data not shown).

Obesity and potential interactions

When stratified by TRUS volume, hypertension status, smoking, alcohol consumption, or baseline testosterone or DHT levels, obesity remained associated with increased risk of high-grade disease and decreased risk of low-grade disease in all subsets and there were no significant interactions (all $P_{\text{interactions}} > 0.14$), though due to small numbers, in many of these subsets the associations with obesity and outcome were not statistically significant. Results remained the same after accounting for family history of prostate cancer. A sensitivity analysis excluding men with DRE suspicious for prostate cancer at baseline showed that results were largely unchanged, in that obesity remained associated with higher risk of high-grade and lower risk of low-grade prostate cancer. When stratified by the median

age of 63, obesity was associated with lower risk of low-grade disease in both younger and older men, though the association in younger men was not statistically significant ($P = 0.11$). However, obesity was only associated with high grade in older men (OR, 1.55; 95% CI, 1.14–2.11; $P = 0.005$) and not in younger men (OR, 0.95; 95% CI, 0.64–1.42; $P = 0.82$; Table 3). The formal test of interaction between age and obesity for predicting high-grade disease approached but did not reach significance ($P_{\text{interaction}} = 0.06$).

Discussion

Studies on the association between obesity and prostate cancer risk have rendered conflicting results (2,8,11–23), though increasingly it is becoming apparent that obesity may be linked with fewer nonaggressive cancer, but increased risk of aggressive cancer (4). Although the mechanisms explaining these observations are not clear,

Table 3. ORs for the association between obesity and risk of overall, low-grade, and high-grade prostate cancer in the REDUCE study, stratified by median age

	Overall Cancer ^b		Low-grade cancer ^b Gleason (≤ 6)		High-grade cancer ^b Gleason (≥ 7)	
	OR ^a (95% CI)	P	OR ^a (95% CI)	P	OR ^a (95% CI)	P
Obesity predicting cancer grade						
Age <63	0.85 (0.68–1.06)	0.15	0.81 (0.62–1.05)	0.11	0.95 (0.64–1.42)	0.82
Age ≥ 63	0.99 (0.80–1.22)	0.90	0.77 (0.60–0.99)	0.04	1.55 (1.14–2.11)	0.005

NOTE: $P_{\text{interaction}}$ between obesity and age is 0.12 for overall prostate cancer, 0.8 for low-grade prostate cancer, and 0.06 for high-grade prostate cancer.

^aAdjusted for age, BMI, race, PSA, DRE findings, TRUS volume, and study treatment arm.

^bReferents were nonobese men (BMI <30 kg/m²) and no cancer.

data suggest that obesity is associated with lower PSA levels (6,7), which could lead to fewer cancers detected, thereby confounding any analysis of the association between obesity and prostate cancer risk. To address this, we tested the association between obesity and prostate cancer in the REDUCE study (10), in which the vast majority of men underwent per-protocol biopsies regardless of PSA levels. Herein, we found that obesity was associated with reduced risk of low-grade and increased risk of high-grade prostate cancer. These findings provide further support for the hypothesis that obesity is a risk factor for high-grade disease independent of PSA levels and other clinical covariates.

An important finding from our study was that while overall, obesity was unrelated to prostate cancer risk, it was selectively linked with increased high-grade and decreased low-grade disease. Of note, prior studies have seen obesity linked with fewer low-grade cancers and more high-grade cancers (8,18,21). However, these studies were limited by ascertainment bias in that not all men had equal opportunities for cancer detection. The study most similar to ours used data from the Prostate Cancer Prevention Trial, a randomized trial of finasteride versus placebo for prostate cancer prevention (8). They examined 10,258 men who underwent end-of-study biopsy and showed that obesity (top vs. bottom quartile) was associated with 18% lower risk of low-grade but 29% higher risk of high-grade prostate cancer (8). However, within the Prostate Cancer Prevention Trial almost 40% of men refused the end-of-study biopsy (8). In this study, nearly 83% of men underwent a biopsy, and <7% had a protocol-independent biopsy, suggesting that the vast majority had biopsies obtained independent of PSA. Thus, REDUCE provides a unique opportunity to examine the association between obesity and prostate cancer risk independent of the association between obesity and PSA. Furthermore, all biopsies were read by a single pathologist. Also, all serum analyses were done by a central laboratory eliminating variations that occur among different laboratories. The availability of key covariates, including lifestyle factors (smoking, alcohol) and comorbidities, allowed us to better assess the association between obesity and prostate cancer risk independent of these confounders. Therefore, this analysis provides strong evidence that obesity is fundamentally linked with higher risk of high-grade but lower risk of low-grade prostate cancer.

These disparate results between low- and high-grade diseases may explain much of the confusion about obesity and prostate cancer risk seen in the literature. For example, in the United States, where PSA screening is common and most prostate cancers are low-grade, this would explain the inverse association seen between obesity and prostate cancer risk in many studies (8,18,21,22). Alternatively, in Europe where PSA screening is less common and many cancers are more advanced at diagnosis, this could explain why obesity is linked with increased prostate cancer risk (11,16). Indeed, a recent meta-analysis found

obesity to be linked with increased prostate cancer risk in Europe, but null associations in the United States (24).

As reviewed in ref. (1), there are several mechanisms by which obesity could be biologically linked with aggressive prostate tumors while decreasing the risk of low-grade tumors. However, the individual contribution of each factor is unknown. For example, obese men tend to have higher serum insulin, IGF1, and leptin concentrations while having lower adiponectin levels, all of which have been linked with prostate cancer in some studies (25). In addition, obese men tend to have lower serum testosterone, which some studies have linked with an increased risk of aggressive poorly differentiated disease (26) but a decreased risk of localized well-differentiated prostate cancer (27). Finally, obesity is linked with excess inflammation, which in theory could be antitumor for indolent tumors, while generating free radicals leading to DNA damage thus promoting the development of more aggressive tumors.

Our study was limited by missing data on key characteristics such as sex hormone-binding globulin levels and free androgen levels, which may be more biologically relevant in obese men. However, adjusting for serum androgens had no influence on our results. All men in this study had a negative baseline pre-study biopsy. It is possible that obesity influenced the risk of cancer detection on this initial biopsy, that is, obese men are at increased risk of having a missed high-grade cancer and by only examining men with a negative biopsy, we are missing the true effect of obesity on prostate cancer risk, though as noted our results are consistent with other studies that only examined initial biopsies (8,28) and had longer follow-up (8). Obese men had a larger prostate size, which we previously showed is associated with a lower rate of undergrading at the time of biopsy (29). As such, this fact coupled with the fact that we adjusted for prostate volume, supports the idea that the association between obesity and high grade is not simply a prostate volume artifact. All men in this study had an elevated PSA. Thus, though once enrolled on the study, biopsies were generally independent of PSA, enrollment on the study was not. As such, this creates another selection bias. As data were unavailable regarding the men with a negative biopsy but who did not enroll in REDUCE due to not meeting the PSA entry criteria, it is unclear how this may have affected our results. Also, though dutasteride can cause prostate volume shrinkage, which in theory could aid in detection of missed cancers, we previously showed that the amount of prostate volume shrinkage was less in obese men (30). Thus, the association between obesity and prostate cancer detection is unlikely to be confounded by dutasteride use. Similarly, dutasteride use has been associated with higher-grade tumors (9). However, there were no significant interactions between dutasteride and obesity, indicating that the association between obesity and high-grade prostate cancer was independent of dutasteride treatment. As such, combining both arms of the REDUCE study merely increased the statistical power of our

analysis. The limited number of men with extreme BMI values restricted our ability to examine the association between extreme BMI values and prostate cancer risk. Also, the number of non-White men in this study was small, limiting our power to examine these men separately. Whether our results apply to non-White men require further study, particularly, future clinical trials should include more men of African descent to test whether obesity is also a risk factor for high-grade prostate cancer among this group. Although the interaction between obesity and age approached significance for high-grade disease, it was not statistically significant. Moreover, in light of the fact that we examined multiple possible interactions, whether these results stem from type I error of multiple testing or other reasons (i.e., residual confounding, biologic, etc.) remain to be determined. Finally, our study outcome was prostate cancer detected on biopsy. Because of the study design of the REDUCE trial, we were unable to address how obesity may influence prostate cancer progression, and this topic requires further study.

In summary, in the REDUCE trial, in which nearly all biopsies were performed regardless of PSA levels, obesity was associated with a reduced risk of low-grade prostate cancer and with an increased risk of high-grade disease. These findings suggest that obesity may have a biologic role in the development of aggressive prostate cancer. Future studies should test whether lifestyle changes, which promote weight loss, can prevent the risk of developing high-grade disease.

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Disclosure of Potential Conflicts of Interest

R. Castro-Santamaria has ownership interest (including patents) in GlaxoSmithKline. G.L. Andriole Jr reports receiving commercial research support from Johnson & Johnson and Medivation, and is a consultant/advisory board member for Augmenix, Bayer Pharmaceuticals, Genomic Health, GlaxoSmithKline, and Myriad Genetics. No potential conflicts of interest were disclosed by the other authors.

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Acknowledgments

The authors wish to acknowledge the dedication of the patients, investigators, data and safety monitoring committee, steering committee, and GSK in the initiation and conduct of the REDUCE study.

Grant Support

This study was supported by GlaxoSmithKline (GSK). Dr. S. Freedland received research support from GSK and NIH K24CA160653. The REDUCE study was funded by GlaxoSmithKline.

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Received July 9, 2014; revised September 4, 2014; accepted September 23, 2014; published OnlineFirst September 27, 2014.

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Cancer Epidemiol Biomarkers Prev 2014;23:2936-2942. Published OnlineFirst September 27, 2014.

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