

Saturated fat intake predicts biochemical failure after prostatectomy

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Previous reports show that obesity predicts biochemical failure after treatment for localized prostate cancer. Since obesity is associated with increased fat consumption, we investigated the role that dietary fat intake plays in modulating obesity-related risk of biochemical failure. We evaluated the association between saturated fat intake and biochemical failure among 390 men from a previously described prostatectomy cohort. Participants completed a food frequency questionnaire collecting nutrient information for the year prior to diagnosis. Because fat and energy intake are highly correlated, the residual method was used to adjust fat (total and saturated) intakes for energy. Biochemical-failure-free-survival rates were calculated using the Kaplan–Meier method. Crude and adjusted effects were estimated using Cox proportional hazards models. During a mean follow-up of 70.6 months, 78 men experienced biochemical failure. Men who consumed high-saturated fat (HSF) diets were more likely to experience biochemical failure ($p = 0.006$) and had significantly shorter biochemical-failure-free-survival than men with low saturated fat (LSF) diets (26.6 vs. 44.7 months, respectively, $p = 0.002$). After adjusting for obesity and clinical variables, HSF-diet patients were almost twice as likely to experience biochemical failure (hazard ratio = 1.95, $p = 0.008$) compared to LSF diet patients. Men who were both obese and consumed HSF diets had the shortest biochemical-failure-free-survival (19 months), and nonobese men who consumed LSF diets had the longest biochemical-failure-free-survival (46 months, $p < 0.001$). Understanding the interplay between modifiable factors, such as diet and obesity, and disease characteristics may lead to the development of behavioral and/or targeted interventions for patients at increased risk of progression.

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The identification of modifiable factors that may influence long-term outcome for prostate cancer (PCa) has considerable potential to reduce morbidity and mortality.^{1–3} Our group and others have reported that obesity is associated with increased risk of biochemical failure after treatment with radical prostatectomy^{4,5} or external beam radiation⁶ for localized disease. Since the prevalence of obesity in U.S. adults has reached epidemic proportions, furthering our understanding of the relationship between obesity-related risk and PCa outcome has become an increasingly important public health issue.

The epidemiological associations between high-fat diets and obesity,^{7–9} and higher fat consumption with increased PCa risk and mortality^{1,10–12} have been well documented. It has been suggested that some types of fat (*i.e.*, monounsaturated) may actually protect against PCa,^{13–15} whereas saturated fat consumption has been more consistently associated with PCa risk, especially advanced disease.^{11,16,17} To evaluate the role that dietary fat intake plays in modulating obesity-related PCa progression, we examined the association between self-reported dietary intake of saturated fat and biochemical failure in a well-defined cohort of PCa patients treated by radical prostatectomy.⁵

Subjects and methods

The study population is a subset of a previously described cohort of 526 patients at The University of Texas M.D. Anderson Cancer Center.⁵ All patients had clinically organ-confined PCa at time of diagnosis and were treated with only prostatectomy. Due to the limited number of African–American and Hispanic partici-

pants, as well as known racial/ethnic variation in diet, we restricted the patient population to Caucasians ($N = 405$). This study was conducted in accordance with the Institutional Review Board, and informed consent was obtained prior to personal interview.

Using standardized questionnaires, demographic information, personal medical history, family history of cancer and other risk factor data were collected as previously described.⁵ The semi-quantitative validated Block food frequency questionnaire (FFQ) (Health Habits and History Questionnaire), modified to incorporate foods commonly consumed in the Southwestern diet, was used to collect usual dietary intake for the year prior to diagnosis.¹⁸ Patients were asked to report the average frequency of intake (per day, week, month or year) and usual portion size (*i.e.*, small, medium or large, relative to a defined medium portion) for ~180 food items. Approximately 80% of patients had the FFQ administered within 6 months of registration at M.D. Anderson. We did conduct a subset analysis and found no differences in range of responses between those who completed the FFQ within 6 months and those who completed it later. All patients were instructed by trained interviewers to provide answers for usual diet for the year prior to diagnosis. FFQs were reviewed by registered dietitians for completeness and acceptability. Only patients who completed the risk factor questionnaire and reported daily caloric intake between 600 and 5,000 kcal/day were included in this study ($N = 390$). DIETSYS+Plus (Version 5.9) along with the USDA National Nutrient Database for Standard Reference (Release 17) was used to calculate average daily intake of macro-nutrients and micro-nutrients for each individual.

Body mass index (BMI, kg/m²) was calculated from self-reported height and weight. Obesity was defined according to the National Heart, Lung and Blood Institute guideline of BMI ≥ 30.0 kg/m². Leisure time physical activity was categorized based on participant response to “the year before your diagnosis, how often did you do physical activities such as jogging, biking or brisk walking (long enough to get sweaty)?” Family history of PCa in first-degree relatives was defined as PCa diagnosed in father, brother or son.

Clinico-pathologic characteristics were abstracted by trained study personnel from medical records using standardized forms and included prostatectomy Gleason score, pathological stage (including surgical margin status and seminal vesicle involvement) and preoperative PSA levels.⁵ Tumors were classified based on pathological stage as pT2 (organ-confined) and pT3 (extraprostatic extension +/- seminal vesicle invasion). Time to progression was measured from date of prostatectomy to date of 1st detectable prostate specific antigen (PSA) test (≥ 0.1 ng/ml, biochemical failure) or last date the patient was known to have no evidence of disease (censor).

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Statistical analysis

Categorical variables, such as family history, history of diabetes, leisure-time physical activity, prostatectomy Gleason score, margin status and pathological stage were analyzed using χ^2 or Fisher's exact tests to evaluate differences in the distribution of the clinical, demographic and risk factor data. Continuous variables, such as age, BMI, education and dietary intake, were compared between groups using Student's *t*-tests. Since total and saturated fat intake were highly correlated ($r = 0.89$ and $r = 0.86$, respectively, $p < 0.001$ for both) with total daily energy intake, we energy-adjusted fat consumption using the residual method.¹⁹ Energy-adjusted total and saturated fat intakes were categorized into quartiles for initial analyses. Since risk of progression was significantly higher among men in the upper quartiles of total and saturated fat consumption (*i.e.*, Q4) as compared to those in the lower 3 quartiles (*i.e.*, Q1–Q3), analyses were conducted by dichotomizing intake (high intake = Q4, lower intake = Q1–Q3). To assess whether total fat or saturated fat was a better predictor of outcome, parallel predictive models were constructed. Total energy intake (kcal) was also evaluated as an independent predictor of outcome modeled as a continuous variable. The Gleason scores from prostatectomies were analyzed in 4 categories: 6, 7 (3 + 4), 7 (4 + 3) and ≥ 8 . The distribution of preoperative PSA was skewed to the right, therefore, all values were log-transformed prior to analysis, and PSA was analyzed as a continuous variable.

Biochemical-failure-free survival rates were calculated using the Kaplan–Meier method, and log-rank tests were used to evaluate statistical significance. Univariate Cox proportional hazards models allowed us to evaluate the crude effects of each factor of interest. Variables with $p \leq 0.10$ were evaluated for inclusion in a multivariable model that simultaneously adjusted for all other included variables. In a forward stepwise manner, the multivariable model was constructed; and 95% confidence intervals were estimated for all point estimates using 2-sided testing (SPSS version 12.0, Chicago, IL). The final multivariable model only includes factors shown to significantly improve the predictive value.

Results

This subset of 390 men was representative of the previously described larger cohort with respect to age and clinico-pathologic characteristics.³ Table I shows patient characteristics for men by level of saturated fat intake [high saturated fat diets (HSF) and lower in saturated fat (LSF)]. Compared to men who consumed LSF diets, men who consumed HSF diets were younger (59.4- vs. 61.2-years-old, respectively; $p = 0.03$) and had higher BMIs at diagnosis (28.4 vs. 27.3 kg/m², respectively; $p = 0.03$) (Table I). There were no statistically significant differences in clinico-pathologic characteristics (*i.e.*, prostatectomy Gleason score, PSA, or pathological stage), family history of PCa, education, history of diabetes or physical activity between these 2 groups. As expected, men consuming HSF diets, also consumed more calories (2,292 vs. 2,088 kcal/day, respectively, $p = 0.04$) and total fat (102 vs. 73 g/day, respectively, $p < 0.001$) compared to men who ate LSF diets (Table I). The top contributors to daily intake of saturated fat for this patient population were beef steaks, cheese and cheese spreads, hamburgers and cheeseburgers, eggs, ice cream and salad dressing/mayonnaise.

During the follow-up period (mean = 97.3 months), 20% of the patients with pathologically organ-confined disease experienced biochemical failure. Biochemical failure-free survival was estimated using Kaplan–Meier survival methods stratified by saturated fat intake (Fig. 1a). Men who ate HSF diets were significantly more likely to experience biochemical failure ($p = 0.006$), and had significantly shorter biochemical failure-free survival than men who consumed less saturated fat (26.6 vs. 44.7 months, respectively, $p = 0.004$). Five years after surgery, about 65% of men who consumed HSF diets had no evidence of disease compared to 80% of men who consumed LSF diets. Initial analyses of the risk of progression indicated that men in the 2nd and 3rd quartiles of energy-

TABLE I – PARTICIPANT CHARACTERISTICS

Variable	Low saturated fat (N = 293)	High saturated fat (N = 97)	p-value
Age (mean \pm SD)	61.2 \pm 6.8	59.4 \pm 7.3	0.03
Education (years, mean)	15.3	15.4	0.89
+ Family history of PCa in FDR ¹	58 (19.8)	26 (26.8)	0.15
BMI at Dx (kg/m ² , mean)	27.3	28.4	0.03
Diabetes diagnosis	11 (4.0)	8 (8.4)	0.09
Leisure time physical activity			
1+ times/wk	218 (74.4)	65 (67.7)	
Few times/m	33 (11.3)	10 (10.4)	
Rarely/Never	42 (14.3)	21 (21.9)	0.22
Gleason score			
6	73 (24.9)	30 (30.9)	
7 (3 + 4)	90 (30.7)	20 (20.6)	
7 (4 + 3)	64 (21.8)	23 (23.7)	
8	66 (22.5)	24 (24.7)	0.27
PSA > 10 ng/ml	56 (19.6)	20 (21.7)	0.65
+ Surgical margin	41 (14.2)	18 (18.8)	0.28
pT3/T4	76 (26.1)	30 (31.3)	0.33
Calories (kcal/day)	2087.9	2292.1	0.04
Fat (g/day)	73.1	101.6	<0.001
Saturated fat (g/day)	23.4	37.2	<0.001
Unsaturated fat (g/day)	49.6	64.4	<0.001
% Energy fat	31.0	39.6	<0.001
% Energy saturated fat	9.9	14.5	<0.001
PCa progression (%)	17.7	26.8	0.05

¹FDR, first-degree relatives.

adjusted total and saturated fat intake had no appreciable change in risk compared to the lowest quartile. For this reason, fat intake (both total and saturated fat) were dichotomized as Q4 vs. Q1–Q3.

Using Kaplan–Meier methods, we evaluated the combined effects of obesity and saturated fat consumption (Fig. 1b). Men who were both obese and consumed HSF diets had the shortest biochemical failure-free survival (19 months), and nonobese men who consumed LSF diets had the longest biochemical failure-free survival (46 months; $p < 0.001$). Nonobese men who ate HSF diets and obese men who ate LSF diets had intermediate progression-free survival times (29.4 and 41.5 months, respectively). Approximately 85% of nonobese men on LSF diets were biochemical failure-free at 5 years after surgery, compared to 70% obese on LSF and about 65% of nonobese and obese men on HSF diets. The interaction between saturated fat intake and obesity was not statistically significant ($p = 0.99$).

We used Cox proportional hazards models to simultaneously adjust for relevant clinico-pathologic variables in a multivariable Cox proportionate hazards model (Table II). We found that energy-adjusted HSF diet remained an independent predictor of biochemical failure in our final model; PCa patients who consumed HSF diets were almost twice as likely to experience biochemical failure compared to men who ate less saturated fat (HR = 1.98, $p = 0.006$). Increased BMI (continuous) was modestly associated with increased risk of BF (HR = 1.05, $p = 0.05$). Since lack of physical activity may be associated with increased BMI and consuming poorer diet (*i.e.*, diet high in saturated fat), we evaluated the predictive utility of including leisure-time physical activity in the multivariable model; however, physical activity did not improve the overall fit of the model and was not included in the final model. Multivariable analyses indicated that inclusion of energy-adjusted saturated fat intake explained a greater proportion of variance as indicated by the log likelihood of that model compared to the model including total energy intake. Saturated and total fat intake were significantly correlated ($r = 0.95$, $p < 0.001$). However, saturated fat intake explained significantly more overall variance in the model compared to total fat. The addition of total fat intake into the multivariable model with saturated fat intake had no appreciable impact on the overall goodness of fit of the model and was not included.

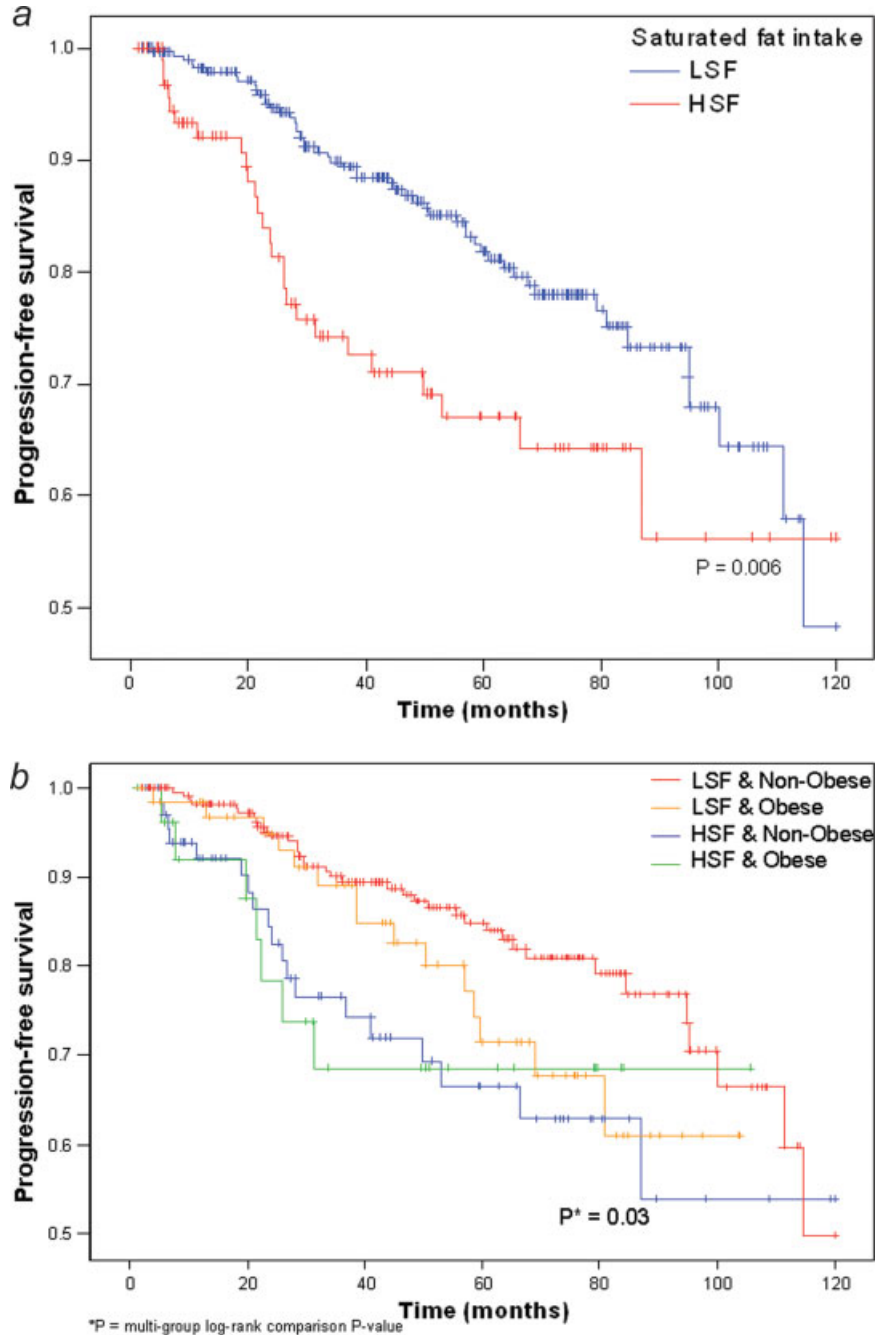


FIGURE 1 – (a) Progression-free survival by saturated fat intake (low vs. high) (LSF = low saturated fat intake; HSF = high saturated fat intake), (b) Progression-free survival by saturated fat intake and BMI (Obese = BMI > 30 kg/m²; Non-obese = BMI < 30 kg/m²), (c) Mean time to progression in months by saturated fat intake and BMI.

c

Saturated Fat	BMI	Mean time to progression (months)
Low	Non-obese	45.9
Low	Obese	41.5
High	Non-obese	29.4
High	Obese	19.2

In initial multivariable models, energy intake alone was evaluated as a potential predictor of failure. Parallel models incorporating the same covariates and either total energy intake or energy-adjusted saturated fat intake were constructed and compared; the model with energy-adjusted saturated fat explained

more variance in the data and was better at predicting outcome compared to the one with total energy intake. In contingency table analysis, no association was found between energy-adjusted saturated fat intake and total energy intake. The inclusion of energy in the multivariable model neither significantly improved

TABLE II – MULTIVARIABLE MODEL OF BIOCHEMICAL FAILURES

Variable	Hazard ratio	95% CI
Without energy		
High saturated fat intake	1.95 ¹	1.19–3.19
BMI (kg/m ² , continuous)	1.06 ¹	1.00–1.12
With energy		
High saturated fat intake	1.90 ²	1.16–3.11
BMI (kg/m ² , continuous)	1.06 ²	1.00–1.12

¹Adjusted for pathologic stage, surgical margin involvement and Gleason score. ²Adjusted for pathologic stage, surgical margin involvement, Gleason score and total energy intake.

the fit of the model nor affected the point estimates (Table II); therefore energy intake was removed from the final model.

Discussion

Our results showed that high prediagnostic saturated fat intake was associated with a 2-fold increased risk of biochemical failure in this cohort of 390 Caucasian men with localized PCa treated with prostatectomy. The multivariable model indicated that this increase in risk of biochemical failure was independent of the increased risk associated with obesity, and both obese and nonobese men who consumed HSF diet had shorter biochemical failure-free survival.

Some epidemiological studies found a direct association between saturated fat intake and PCa risk and prognosis, especially in advanced disease,¹⁶ suggesting that saturated fat may play a role in PCa prognosis. However, not all studies have adjusted for the effects of total energy intake, and the associations or lack thereof reported in these studies may be partially attributable to residual confounding. Additionally, our data support the findings reported by Meyer *et al.* that prediagnostic HSF intake was associated with increased PCa mortality.¹¹ However, to our knowledge, no studies have evaluated the combined effects of both energy-adjusted saturated fat intake and obesity as predictors of PCa progression.

The mechanisms by which these associations affect PCa prognosis have not been established, although some studies suggest that alterations in insulin metabolism may be involved.²⁰ In overweight and obese nondiabetic men, diets high in saturated fat were shown to induce insulin resistance, which has been suggested to play a role in prognosis.²¹ Additionally, it has been shown that men, whose diets were highest in saturated fat had the highest levels of IGF-1 and lowest levels of IGFBP-3 compared to men who ate diets lower in saturated fat.²² Castrated xenograft mice injected with LAPC-4, an androgen-sensitive PCa cell line, and fed an isocaloric low-fat diet had significantly lower serum levels of insulin and IGFBP-1/-2 as well as slower PCa progression compared to similarly treated mice on high-fat diet.²⁰

Another plausible mechanism by which saturated fat may influence PCa progression involves heterocyclic amine consumption since several key contributors to saturated fat intake (*i.e.*, beef steaks and hamburgers/cheeseburgers) are known to have high levels of heterocyclic amines. These foods are often prepared using high-heat generating methods, such as grilling or broiling, which has been shown to significantly increase dietary intake of heterocyclic amines, particularly, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), previously demonstrated to have carcinogenic properties. Human prostate tissue is capable of activat-

ing heterocyclic amines that can then bind to DNA and form adducts, which have been associated with prostate carcinogenesis.²³ Additionally, PhIP-DNA adducts levels, a quantitative measurement of PhIP exposure, have been demonstrated to show an association with greater tumor volume and higher Gleason score among African-Americans,²⁴ both of which have been shown to be associated with PCa progression. Higher PhIP intake has been significantly associated with increased PSA levels, which is also a predictor of PCa outcome.²⁵ We were unable to evaluate heterocyclic amine consumption since information on cooking methods was not collected; however, future studies are being designed to collect and incorporate these data.

Sex hormone levels have been shown to be influenced by saturated fat intake. Dietary intervention studies in healthy men have shown that a low-fat diet decreased androgen levels both in serum and urine²⁶ and a high fat diet increased plasma and urinary testosterone and DHEA-S.²⁷ These results demonstrate the ability of short-term changes in fat intake to directly affect the hormonal milieu known to play a key role in the natural history of PCa.²⁸ Overall, the evidence suggests that saturated fat might affect PCa prognosis through several inter-related mechanisms and other dietary components may act in concert or discordance.

This study has some limitations. Nutritional data were collected at the time of study enrollment, and we do not have quantifiable information about how patients changed their diets since diagnosis. There is potential for measurement error since the FFQ is semiquantitative; however, this error should be minimized as we used the data from the FFQs simply to categorize men as high or low consumers of nutrients rather than compare absolute values. Our patient population was limited to Caucasians, as we did not have sufficient power to evaluate inter-racial/ethnic variation in dietary intake in conjunction with progression *vs.* no-progression.

On the other hand, this study has several strengths. The patients comprising our cohort were all diagnosed with clinically localized disease, received the same treatment and did not have adjuvant therapy postoperatively prior to biochemical failure. Since all participants in this study are cancer patients interviewed at baseline (*i.e.*, prior to biochemical failure), there should be no difference in recall between patients who experienced biochemical failure and those who did not. Restricting our patient population to Caucasians limits the effects of inter-racial/ethnic variation in food consumption patterns as well as other lifestyle and genetic differences that may help reduce the effects of confounding.

These results expand upon our previous finding that obesity was associated with increased risk of biochemical failure following prostatectomy, and suggest that saturated fat intake plays a role in PCa progression. After duplicating these findings in a larger patient population from different racial/ethnic groups, future interventions may be designed to decrease consumption of dietary saturated fat to reduce risk of progression in PCa patients as has been done for breast cancer patients.²⁹ It is our hope that these results can be integrated into clinical practice to identify patients at high-risk of progression following definitive therapy. Increasing our understanding of the interplay between modifiable factors, such as lifestyle (*e.g.*, diet) and disease characteristics, may lead to developing targeted interventions for patients at increased risk for biochemical failure.

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