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ABSTRACT & COMMENTARY

Prostatectomy Beats Watchful Waiting in Men Diagnosed With Prostate Cancer in the 1990s

By David Fiore, MD

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Dr. Fiore reports no financial relationships relevant to this field of study.

SYNOPSIS: In men with prostate cancer diagnosed in the 1990s (primarily by digital rectal exam), researchers found that radical prostatectomy offered an average survival benefit of 2.9 years over watchful waiting.

SOURCE: Bill-Axelson A, et al. Radical prostatectomy or watchful waiting in prostate cancer — 29-year follow-up. *N Engl J Med* 2018;379:2319-2329.

This was a follow-up of the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4), in which 695 men were assigned randomly to either radical prostatectomy or watchful waiting from 1989 to 1999 and were followed for up to 29 years. As of 2017, 80% of participants had died, with 181 deaths attributed to prostate cancer (71 in the radical prostatectomy group and 110 in the watchful-waiting group). The cumulative incidence of death at a median of 23 years was 71.9% in the radical prostatectomy group and 83.8% in the watchful waiting group, with a relative risk (RR) of 0.74 for the surgical group and number needed to treat (NNT) of 9.2. The cumulative incidence of death from prostate cancer at 23 years was 19.6% in the radical prostatectomy group and 31.3% in the watchful waiting group (RR for the complete follow-up period, 0.55; NNT, 8.5).

Metastases were diagnosed in 92 men in the radical prostatectomy group and 150 men in the watchful waiting group (RR, 0.54 for the radical prostatectomy group; NNT, 6.0). In men who underwent radical prostatectomy, extracapsular extension and higher-grade Gleason scores were associated with a worse prognosis. Thirty-eight men with extracapsular extension died from prostate cancer compared with

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nine men without extracapsular extension (RR, 5.21). Compared to men with a Gleason score of 6, a score of 7 (4+3) was associated with a five times higher risk of prostate cancer death (RR, 5.73). A Gleason score of 8 or 9 was associated with more than a 10 times higher risk of death (RR, 10.63).

■ COMMENTARY

This is an important study offering new insight on the progression of prostate cancer and the effect of treatment on long-term outcomes. However, there are a few major caveats, including when this study started and how diagnosis and management of prostate cancer have changed. Critically, only 18% of cancers were found by screening, and only 12% of patients had nonpalpable T1c tumors at the time of screening. This is in stark contrast to the situation in the United States, where most prostate cancers are detected by screening and 80% of prostate cancers were localized (1999-2006).[1]

In the United States, the authors of two studies compared radical prostatectomy to observation. Even after 20 years, those researchers failed to find a benefit from surgery.[2,3] In addition, "watchful waiting" is distinct from "active surveillance" (also called "active monitoring"), which is now the preferred alternative to immediate surgery for nonaggressive prostate cancers in the United States.

Another major limitation of this study is that the authors did not report harms from treatment. Rates of erectile dysfunction following radical prostatectomy range from 14-85% (too wide a range to be useful in counseling), with best estimates in high-quality studies averaging closer to 75%.[4] Rates of incontinence, which can be debilitating for otherwise healthy men, run about 20%.[5] Unfortunately, these rates are not much lower after robotic surgery.

The NNT statistics were impressive, and this study received a lot of attention in the lay press. Still, this study does not really change the equation about when or whether to order a PSA for screening purposes, nor does it help much when deciding between active monitoring and radical prostatectomy. What this research does tell us is that in men with advanced prostate cancer and a longer life expectancy, radical prostatectomy offers both survival and disease-free survival benefits. ■

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ABSTRACT & COMMENTARY

Low-Carbohydrate Diet Increases Energy Expenditure

By Joseph E. Scherger, MD, MPH

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Dr. Scherger reports no financial relationships relevant to this field of study.

SYNOPSIS: Consistent with the role of insulin and carbohydrate intake, a low-carbohydrate diet increases energy expenditure and facilitates the maintenance of weight loss.

SOURCE: Ebbeling CB, et al. Effects of a low carbohydrate diet on energy expenditure during weight loss maintenance: Randomized trial. *BMJ* 2018;363:k4583.

Ebbeling et al conducted this randomized, controlled trial at two sites in Framingham, MA, between August 2014 and May 2017. The group evaluated the recent realization that with most weight loss diets, hunger increases and energy expenditure decreases. These physiologic adaptions work against long-term weight loss. Most standard weight loss diets are calorie-restricted, with about 60% of calories coming from carbohydrates. The purpose of the study was to assess metabolic expenditure at rest using three different carefully controlled diets that were high in carbohydrates (60% of calories), medium in carbohydrates (40% of calories), and low in carbohydrates (20% of calories) during the maintenance phase of a weight loss program. Investigators recruited 164 subjects aged 18-65 years. Participants started the study following the same diet to accomplish 2 kg of weight loss. The composition of this "run-in" diet was 45% carbohydrates, 30% fats, and 25% proteins. The subjects were randomized to one of the three diet types. Protein intake was controlled to 20% of calories in all three groups so that subjects on 60% carbohydrates received 20% of calories from fat, those on 40% carbohydrates received 40% from fat, and those on 20% carbohydrates received 60% from fat. The testing phase lasted 20 weeks. The results showed that subjects on the lower-carbohydrate diets showed a linear increase in energy expenditure at rest and a linear benefit in maintaining weight reduction. Ghrelin, the hormone that increases appetite, was significantly lower in subjects on the low-carbohydrate diet. In addition, insulin levels were lower with low-carbohydrate diets.

■ COMMENTARY

Forty years ago, clinical guidelines in nutrition moved to a low-fat, complex carbohydrate diet. The American food supply became awash in refined carbohydrates. The "green revolution" that started in the 1970s shifted American agriculture to wheat and corn as dominant crops for human consumption and feed for animals. Since 1980, there has been an epidemic of overweight, obesity, and type 2 diabetes.[1] By 2001, scholars began to question the low-fat recommendations and suggested that sugar and carbohydrates were the real problem. Despite resistance from the food industry that makes its greatest profits from high-carbohydrate foods, scientific evidence is growing that carbohydrates drive hunger and weight gain.[2] We have learned that once obtained, the body can hold on to fat and get it back once lost through changes in metabolism.[3] Research has shown that the most effective way to break this problem and maintain low weight is through low-carbohydrate nutrition and remaining in a state of ketosis for at least part of the day. This is facilitated by intermittent fasting, which further lowers insulin secretion. Low-carbohydrate nutrition and weight loss programs are emerging, including in academic centers. Look for programs in your area that can provide this patient education and incorporate low-carbohydrate nutrition into your practice. ■

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BRIEF REPORT

Helicobacter pylori: A Mini Primer

By Carol A. Kemper, MD, FACP

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Dr. Kemper reports no financial relationships relevant to this field of study.

SOURCE: Siddique O, et al. *Helicobacter pylori* infection: An update for the internist in the age of increasing global antibiotic resistance. *Am J Med* 2018;131:473-479.

Like every other infection, *Helicobacter pylori* (HP) is increasingly drug resistant. Estimated failure rates are 5-10%, even after receipt of two different antimicrobial regimens. Failures most often are due to resistance to clarithromycin (which may be as high as 30% in some countries and in some parts of the United States) and levofloxacin (which also may be approaching resistance rates of 30% in some parts of the United States). Physicians need to keep pace with the consequences of this development and newer recommendations. Although the prevalence of HP seems to be decreasing in the United States, at least in higher socioeconomic strata, HP

remains a problem for lower-income groups, travelers to developing countries, and the rest of the world. The prevalence of HP is believed to be > 50% in some parts of the world, especially in Central Asia, Central America, and Eastern Europe.

There are multiple barriers to appropriate testing and treatment. The first barrier is the promotion of testing for HP in patients at risk. HP screening is indicated for anyone with recurring epigastric discomfort, chronic use of nonsteroidal anti-inflammatory drugs, unexplained iron deficiency anemia, and ITP. Any of the "alarm symptoms," such as recurrent vomiting, weight loss, and dysphagia, especially with a family history of gastric cancer, should prompt endoscopy with biopsy and examination for HP.

The second barrier is the type and timing of testing. Tests for active infection include stool antigen testing and the urea breath test (both ≥ 95% sensitive, ≥ 95% specific). But these tests must be performed more than four weeks after the use of any bismuth-containing product or antibiotic, and all proton pump inhibitors (PPI) must be stopped for more than two weeks. Serologic testing is not recommended, as it may remain positive for many years after successful eradication and is associated with a higher false-positive rate.

When selecting a first-line regimen, the patient should be queried about antibiotic use in the past one to two years. Prior treatment with macrolides or levofloxacin may increase the risk of resistance, and a regimen without the respective agent should be selected. In contrast, resistance to amoxicillin, tetracycline, and metronidazole is uncommon (< 2%).

Patients should be counseled that strict adherence to the regimen is necessary. Missed doses may increase the risk of developing resistance during treatment, especially with clarithromycin. Completion of the entire regimen is important to successful eradication. In those who fail a first-line regimen, consider whether the patient is allergic to penicillin and whether clarithromycin or levofloxacin was used in the first regimen. There are two or three options depending on the answers to these questions. For example, for patients who fail a first-line regimen containing clarithromycin, a regimen without clarithromycin should be selected (e.g., amoxicillin, levofloxacin, PPI × 14 days). The management of patients who have failed two regimens is not straightforward. Endoscopy with biopsy and culture for susceptibility testing is recommended, although the organism does not always grow well in culture, and susceptibility testing is not widely available. Empiric treatment with a nonclarithromycin-based regimen (e.g., rifabutin, amoxicillin, PPI × 10 days) in those previously treated with clarithromycin can be attempted. A levofloxacin-containing regimen can be used in those not previously treated with fluoroquinolones. Increasing the dose of the PPI, or using newer, more potent PPIs, may be helpful. Finally, confirming eradication four weeks or more following completion of treatment is mandatory. ■

BRIEF REPORT

Alcohol Use: No Safe Level

By Ellen Feldman, MD

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Dr. Feldman reports no financial relationships relevant to this field of study.

SYNOPSIS: A systematic analysis of data from the Global Burden of Disease Study 2016 on alcohol-linked disorders and patterns of alcohol use over 25 years worldwide found there is no safe level of alcohol consumption.

SOURCE: GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2018;392:1015-1035.

Do the health benefits of alcohol balance or override the health risks of alcohol consumption? This and related questions spurred an innovative and comprehensive approach to analyzing data obtained from the Global Burden of Diseases, Injuries and Risk Factors Study (GBD) 1990-2016. Collaborators analyzed findings obtained from 195 countries and territories over this 26-year period and used several newer epidemiological approaches to understand the prevalence of alcohol use, the health risks associated with alcohol use (including disability and development of alcohol-related diseases and death), and any health benefits associated with alcohol use. The findings are sobering. Among the worldwide population ages 15-49 years, alcohol was the No. 1 cause of disability-adjusted life years (DALY) and the leading risk factor for death, accounting for nearly 10% of deaths in this group. Among all age groups in 2016, 2.8 million deaths worldwide were linked to alcohol use. When looking at death and DALY among all age groups globally, alcohol was the seventh-leading risk factor. Although alcohol consumption rates vary with geographical boundaries, in 2016, more than 2 billion people

worldwide consumed alcohol; about 63% were male. Kuwait, Iran, and Palestine emerged with the lowest death rates related to alcohol use among persons 18-49 years of age (0.3-0.4 per 100,000 people), while Lesotho, Russia, and the Central African Republic reported the highest death rates attributable to alcohol in this age group (108.8-145.3 per 100,000 people).

Cardiovascular disease, specific cancers, communicable diseases such as tuberculosis, intentional and unintentional injuries, as well as transportation-related injuries were among the 23 disorders and health states associated with alcohol use. The study authors examined health benefits associated with alcohol, including investigating evidence linking alcohol consumption to protection from ischemic heart disease and diabetes in women.[1,2] With a newer approach to the available data, the collaborators concluded that even low levels of alcohol consumption increase the risk of specific cancers in women and that potential health benefits likely are offset by this association. According to the data analysis, the level of consumption minimizing health risk is zero. Notably, researchers did not distinguish between types of alcohol consumed or relative content of drinks consumed (percent alcohol was not noted.) Perhaps doing so would have allowed more meaningful results, but at this point there are no data to support or refute this possibility. Arguably, the most meaningful critique of this study is that it was strictly observational; results must be interpreted with due respect to the methodology.

The authors, who were from more than 40 countries, made a case for revising health guidelines. The study collaborators noted that the current recommendation to consume one to two drinks daily for health benefits is no longer valid and should be revised to reflect "the safest level of drinking is none." They added that policies addressing alcohol consumption at the population level (such as taxation of alcohol products and cultural modifications) will be most effective at combating the associated health risk. In a related development, the National Institutes of Health's Moderate Alcohol and Cardiovascular Health trial (a study about the health benefits of moderate alcohol consumption) ended in 2018 in part because of methodological concerns that the study design failed to address the potential health risks of moderate alcohol consumption.[3]

While advocating abstinence from alcohol may seem unrealistic and excessive, it is within our purview and responsibility to stop promoting drinking for health benefits. This does not mean that we should counsel all patients to stop drinking, but we should be clear that health benefits from alcohol consumption may be overstated and outweighed by risks. Everyday lifestyle and behavior is an essential part of a wellness plan. Providing patients with accurate information about the findings of this study allows each individual to develop a nuanced and comprehensive approach to healthy living. ■

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ABSTRACT & COMMENTARY

Should Acute Appendicitis Be Managed Without Appendectomy?

By Richard R. Watkins, MD, MS, FACP, FIDSA

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Dr. Watkins reports no financial relationships relevant to this field of study.

SYNOPSIS: A retrospective cohort study that used national insurance claims data revealed patients with acute appendicitis who were treated nonsurgically experienced higher rates of complications and higher overall care costs.

SOURCE: Sceats LA, et al. Nonoperative management of uncomplicated appendicitis among privately insured patients. *JAMA Surg* 2018; doi: 10.1001/jamasurg.2018.4282. [Epub ahead of print].

The management of acute appendicitis without appendectomy has generated considerable interest among clinicians and patients in recent years. Several clinical trials have shown similar outcomes with appendectomy and nonsurgical management (i.e., antibiotics). However, deciding which patients should be managed without surgery has been challenging, and long-term data are scarce. Sceats et al aimed to clarify these issues by comparing outcomes for patients with acute appendicitis who underwent appendectomy

to those who received nonsurgical management. The study was a retrospective cohort analysis that used information from a claims database of 40-50 million privately insured patients, mainly with large employer-sponsored health plans. Researchers included patients who received an admission diagnosis of acute appendicitis between Jan. 1, 2008, and Dec. 31, 2014. Patients were divided into two groups: those who underwent appendectomy based on the presence of procedure codes and those who received nonsurgical management.

The primary outcomes were rates of short-term (< 30 days) complications (i.e., ED visits, all-cause readmissions, appendicitis-associated readmissions, occurrence of abdominal abscess, and *Clostridium difficile* infection), and long-term (> 30 days) complications (i.e., readmission for small bowel obstruction, incisional hernia, and diagnosis of appendiceal cancer).

The researchers conducted a post hoc analysis on the nonsurgical group to evaluate the rate of management failure and the rate of appendicitis recurrence. Instead of using propensity score matching to balance the two groups, the authors used coarsened exact matching (CEM) because of a presumed bias in patients selected for nonsurgical management. This technique is based on forecasting after pruning observations such that the covariate distributions between the two groups improve in the data that remain.

Researchers identified 58,329 patients with acute appendicitis during the study period, of whom 55,709 underwent appendectomy and 2,620 received nonsurgical management. There were significant differences between the appendectomy and nonsurgical groups in terms of age (31.8 years vs. 34.2 years, respectively; $P < 0.001$) and the grouped Charlson comorbidity index ($P < 0.001$). Regarding short-term complications, patients who underwent nonsurgical management experienced significantly higher all-cause readmissions and appendicitis-associated readmissions ($P < 0.001$). Moreover, patients who received nonsurgical management were significantly more likely to develop an abdominal abscess than those who underwent appendectomy (2.3% vs. 1.3%, respectively; adjusted odds ratio [aOR], 1.42; 95% confidence interval [CI], 1.05-1.92). The results indicated no significant differences in the rates of ED visits or *C. difficile* infection.

Among long-term complications, those patients managed nonsurgically showed higher rates of appendiceal cancer compared to those who underwent appendectomy (aOR, 4.07; 95% CI, 2.56-6.49). There were no significant differences in the rates of admission for small bowel obstruction or incisional hernias. The length of stay was slightly longer in the nonsurgical group (1.7 days vs. 1.6 days), and these patients also logged more follow-up visits for appendicitis in the year following hospital discharge compared to those who underwent appendectomy (1.6 visits vs. 0.3 visits; $P < 0.001$). The nonsurgical group paid lower mean costs for index hospitalization. However, when the total cost of care associated with appendicitis was evaluated, nonsurgical management was more expensive ($14,934 vs. $14,186). The overall failure rate of nonsurgical management was 3.9%, and the median time from the initial diagnosis to management failure or recurrence was 42 days (range, 8-125 days).

■ COMMENTARY

This is an interesting and important study because it informs clinicians about managing acute appendicitis nonsurgically in a real-world setting (i.e., outside of a clinical trial). Of the 4.5% of patients managed nonsurgically, only 3.9% required an appendectomy during a mean follow up of 3.2 years. This is in contrast with results from randomized clinical trials, in which such rates were approximately 27%. The reason for this discrepancy is uncertain and might be a result of the patient populations studied, although an alternative explanation is that patients in clinical trials are monitored more carefully. Readmission rates, office visits, and complications (including abscess formation and appendiceal cancer) were lower in the operative group. The authors of a recent randomized clinical trial found a high rate of appendiceal cancer in patients treated nonsurgically for peri-appendicular abscess.[1]

Although the cost of the initial hospitalization for acute appendicitis was lower in the nonsurgical group, this benefit was more than offset by the costs that came after, including more office and ED visits. The higher rates of complications also led directly to increased costs, which were 5.5% greater in the nonsurgical group. Moreover, the time out of work that the nonsurgical patients experienced because of their additional visits was an indirect cost that was not factored into the economic analysis.

There were a few limitations to the study. First, the cohorts were significantly different in terms of age and Charlson comorbidity index. Second, the retrospective design makes the presence of unmeasured confounding variables a possibility. Third, there also may have been selection bias in favor of nonsurgical management because this approach often is used when patients are deemed poor surgical candidates. The authors attempted to account for this possibility using the CEM algorithm and multivariate analysis.

Many, if not most, patients would choose to avoid appendectomy if they were told there was a reasonable chance of cure by nonsurgical management. It does

them a disservice if the best available evidence suggests otherwise. Thus, the study by Sceats et al should be taken into account by clinicians (both surgeons and non-surgeons) during conversations with patients who have acute appendicitis about their expectations and possible outcomes. ■

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PHARMACOLOGY UPDATE

Prucalopride Tablets (Motegrity)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

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Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a highly selective serotonin 5-HT4 receptor agonist to treat chronic idiopathic constipation (CIC) in adults. Previously approved members of this pharmacologic class, cisapride and tegaserod, were withdrawn from the market because of higher risks of potential adverse cardiovascular events. Prucalopride has been available in Europe for 10 years. It is marketed as Motegrity.

INDICATIONS

Prucalopride is indicated for the treatment of CIC in adults.[1]

DOSAGE

The recommended dose is 2 mg once daily.[1] For patients with severe renal impairment (creatinine clearance < 30 mL/min), the dose is 1 mg once daily. The tablets may be taken without regard to food. Prucalopride is available as 1 mg and 2 mg tablets.

POTENTIAL ADVANTAGES

Prucalopride offers a drug from a different class and different mechanism of action for the treatment of CIC.

POTENTIAL DISADVANTAGES

The long-term efficacy, particularly in the elderly, has not been established. The most frequently reported adverse reactions (compared to placebo) were headache (19% vs. 9%), abdominal pain (16% vs. 11%), nausea (14% vs. 7%), and diarrhea (13% vs. 5%).[1]

Asian patients reported a higher frequency of diarrhea compared to non-Asian patients but lower frequency of other adverse events.[2] There is a warning on the label for increased risk of suicidal ideation and behavior.[1]

COMMENTS

Prucalopride is a selective 5-HT4 agonist that results in the stimulation of colonic peristalsis, increasing bowel motility.[1] Its efficacy was evaluated in six double-blind, placebo-controlled, randomized trials that all included subjects with CIC.[1,2] Five studies lasted 12 weeks each, while the other lasted 24 weeks.

Eligible subjects had a history of chronic constipation (fewer than three spontaneous bowel movement [SBMs] per week) that resulted in a feeling of complete evacuation (CSBM) and one or more of these symptoms: lumpy or hard stools, sensation of incomplete evacuation, or straining at defecation for more than 25% of bowel movements in the preceding three months. Symptoms had to begin more than six months prior to screening. Most subjects were white women, mean age 47 ± 16 years, with a mean duration of constipation of 16 ± 15 years. Subjects were randomized to prucalopride (2 mg daily if age < 65 years and 1 mg with the option to titrate to 2 mg if age ≥ 65 years). Treatment response was defined as an average of ≥ 3 CSBMs per week over the 12-week treatment period.

Five of the six studies revealed statistical advantage for prucalopride, with responder rates ranging from 19-38% vs. 10-18% for placebo. Absolute percent treatment differences ranged from 10-23%. The authors of the 24-week study did not observe statistical difference at either 12 or 24 weeks.[3,4] An integrated analysis of the six studies showed an overall response rate of 27.8% vs. 13.2% for placebo.[5]

Because of the risk of cardiovascular events with a previous member of the same pharmacologic class (tegaserod), cardiovascular safety was assessed with nonclinical data and postmarket pharmacoepidemiologic observational data — mainly European data, since the drug was approved in 2009. Prucalopride showed no significant QTc prolongation, no platelet aggregation, and no evidence of increased risk (excluding a prespecified safety margin of three-fold risk) of major adverse cardiovascular events.[1,3]

CLINICAL IMPLICATIONS

CIC is a common disorder that is more common in women, older individuals, and those of lower socioeconomic status.[6] Treatment of CIC includes a fiber supplement, osmotic and stimulant laxatives, a 5-HT4 receptor agonist, or a prosecretory agent.[6] Currently, prucalopride is the only approved 5-HT4 receptor agonist. Plecanatide and linaclotide are guanylate cyclase-C agonists, and lubiprostone is a chloride channel activator. These agents act by stimulating chloride secretion. Response rates (from placebo) were modest and ranged from 8-17%.[7,8] Furthermore, not all available therapies are either effective or tolerated in all patients.[3]

There are no available comparisons between prucalopride and the other agents. Studies that include laxative-resistant patients would be particularly useful. Only placebo-controlled studies are available; treatment difference between drug and placebo using similar efficacy endpoints appeared to be similar.[3] The cost for prucalopride was not available at the time of this review. ■

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CME QUESTIONS

1. According to the study about prostatectomy, which statement is true?
a. Advanced disease was associated with higher mortality only in the watchful waiting group.
b. Advanced disease was associated with higher mortality only in the radical prostatectomy group.
c. Advanced disease was associated with higher mortality in all patients.
d. Advanced disease was not associated with higher mortality.

2. Which of the following diet ratios is most likely to facilitate sustained weight loss?
a. 60% carbohydrates, 20% fats, 20% proteins
b. 20% carbohydrates, 60% fats, 20% proteins
c. 40% carbohydrates, 40% fats, 20% proteins
d. None of the above

3. Which of the following statements is true about the recommendations from the GBD Alcohol Collaborators?
a. Findings were biased because of difficulty obtaining and comparing information from multiple organizations and diverse geographical locations. All recommendations should be reviewed with this in mind.
b. This review clearly pointed out the risks of alcohol use, but fails to examine the health benefits closely.
c. This review incorporated data regarding both the risks and health benefits of alcohol use and concluded that public health guidelines regarding alcohol use should be revised to reflect that the safest level of drinking is none.
d. This review incorporated data regarding both the risks and health benefits of alcohol use and concluded that public health guidelines should reduce recommendations to one to two drinks weekly rather than daily.