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Obesity and Cancer with Emphasis on Bariatric Surgery

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Introduction

Reported increases in the prevalence of overweight and obesity in the United States and in many countries of the world have resulted in speculation regarding the clinical impact overweight and obesity may have upon associated comorbidities such as diabetes and cardiovascular disease [1]. Contributing to this concern is the finding that in the United States, the prevalence of extreme obesity is increasing at rates greater than moderate obesity [2, 3]. In fact, some reports have proposed that a consequence of increasing obesity rates may be the reversal of the decline in cardiovascular disease [4, 5] and a future generation whose life expectancy may be lower than that of their parents [6, 7]. An equally significant concern related to increasing obesity rates is the associated link between obesity and cancer development [8, 9]. In fact, the topic of obesity and cancer risk has gained increased clinical interest, with greater than 2,000 scientific papers published on the topic [9]. The aim of this chapter is to identify cancers that to date have been associated with obesity and to briefly highlight the leading physiologic theories linking obesity and cancer. The chapter will then explore the validity of national and international recommendations to reduce adiposity, when appropriate, for the purpose of lowering cancer incidence as well as risk for cancer recurrence. Finally, as a result of bariatric surgery the opportunity has been advanced to investigate whether or not long-term voluntary weight loss for overweight or obesity is associated with reduced cancer risk and lower cancer-related mortality. Therefore, the remaining chapter content will review cancer risk and cancer mortality subsequent to bariatric surgery, with brief mention of cancer diagnosis incidental to weight loss surgery.

Obesity and Cancer Risk

Body mass index (BMI; kilograms of body weight divided by height in meters squared) is generally used in cancer studies to categorize normal weight, overweight, and obesity. Adult overweight is defined as a BMI equal to or greater than 25 kg/m^2, and adult obesity is defined as a measured BMI equal to or greater than 30 kg/m^2, with obesity subcategories: class 1 obesity, 30–34.9 kg/m^2; class 2 obesity, 35–39.9 kg/m^2; and class 3 obesity (extreme obesity) ≥40 kg/m^2 [10, 11]. Multiple large population studies, prospective observational studies, and extensive reviews have demonstrated the positive association between increased body fatness and obesity and the risk for specific cancer types [8, 12–27]. An extensive review conducted by the World Cancer Research Fund and American Institute for Cancer Research reported that convincing evidence supports increased body fatness as a cause of adenocarcinoma of the esophagus, and cancers of the pancreas, colorectum, breast (postmenopause), endometrium, and kidney. They also reported greater body fatness to be a probable cause of gallbladder cancer, with limited evidence linking greater body fatness with liver cancer [8]. Accumulating evidence linking obesity with risk of non-Hodgkin lymphoma and ovarian and aggressive prostate cancers was also described. Further, this comprehensive review highlighted convincing evidence linking greater abdominal (central) fatness as a cause of colorectal cancer, with probable evidence demonstrating increased abdominal fatness as a cause of cancers of the pancreas, breast (postmenopause), and endometrium. In contrast, greater body fatness "probably protects" against premenopausal breast cancer [8].

Renehan et al. performed a systematic literature review and meta-analysis for the purpose of evaluating the association between BMI and 20 cancer types with inclusion of sex and ethnic groups [17]. From 221 datasets representing 141 prospective observational studies and over 282,000 incident cases, Renehan et al. reported that a 5 kg/m^2 increase in BMI for men was significantly associated with esophageal adenocarcinoma (RR 1.52, 95 % CI 1.33–1.74; $p<0.0001$) and renal (RR 1.24, 95 % CI 1.15–1.34; $p<0.0001$), thyroid (RR 1.33, 95 % CI 1.04–1.70; $P=0.02$), and colon (RR 1.24, 95 % CI 1.20–1.28; $p<0.0001$) cancers. In women, a 5 kg/m^2 increase in BMI was significantly associated with esophageal adenocarcinoma (RR 1.51, 95 % CI 1.34–1.74;

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$p<0.0001$) and renal (RR 1.34, 95 % CI 1.25–1.43; $p<0.0001$), endometrial (RR 1.59, 95 % CI 1.50–1.68; $p<0.0001$), and gallbladder (RR 1.59, 95 % CI 1.02–2.47; $p=0.04$) cancers [17]. Further, Renehan et al. found "weaker positive associations (RR < 1.20)" for increased BMI and rectal and malignant melanoma cancer for men and, for women, postmenopausal breast, pancreatic, thyroid, and colon cancers [17]. For both sexes, an increasing BMI was associated with a greater risk for leukemia, multiple myeloma, and non-Hodgkin lymphoma [17].

Nonsurgical change in weight status and subsequent cancer mortality has also been reported in large population studies [13, 28, 29]. The most recent of these studies examined cancer mortality of 1.2 million UK women (Million Women Study), recruited between 1996 and 2001 and then followed 7.0 years for cancer mortality [13]. The primary predictor measure was BMI, adjusted for a number of factors such as alcohol intake, physical activity, menopausal status, and hormone replacement status. During the follow-up period, a total of 17,203 cancer deaths were reported. The trend of increasing BMI beyond the reference group (BMI = 22.5–24.9 kg/m^2) was significantly correlated with an increased mortality for the following cancers: adenocarcinoma of the esophagus (RR 2.24, 95 % CI 1.40–3.58), pancreas (RR 1.21, 95 % CI 1.04–1.41), postmenopausal breast (RR 1.36, 95 % CI 1.12–1.66), endometrium (RR 2,46, 95 % CI 1.78–3.39), kidney (RR 1.65, 95 % CI 1.28–2.13), and ovary (RR 1.17, 95 % CI 1.03–1.33); multiple myeloma (RR 1.56, 95 % CI 1.15–2.10); leukemia (RR 1.34, 95 % CI 1.05–1.71); brain cancer (RR 1.17, 95 % 0.95–1.43); and all cancers (RR 1.06, 95 % CI 1.02–1.10) [13]. Although not significant, Reeves et al. reported a decreased premenopausal cancer-related mortality associated with a trend for increasing BMI (RR 0.68, 95 % CI 0.37–1.24) [13].

Potential Mechanisms: Obesity and Cancer Risk

Considerable research effort regarding how obesity influences cancer has generated several published studies and review articles that have postulated biological mechanisms [8, 9, 30, 31]. A recently published book details possible molecular mechanisms relating adipose tissue and cancer, with specific reference to mechanistic links between obesity and specific cancer types [32]. These scientific reports all point to the presence of multiple mechanisms, suggesting "a web of interacting hormones, growth factors, cytokines, and inflammation mediators that promote tumor initiation and growth." [9] In brief, these mechanisms have been classified into three general areas which focus on: chronic inflammation associated with increased release of inflammatory promoters in obese individuals; over-release of steroid-related hormones such as estrogens, androgens and progesterone; and tumor growth promotion, a result of hyperinsulinemia (associated with insulin resistance subsequent to increased body fatness, in particular, abdominal or central obesity) [8, 30, 33]. A perspective/opinion paper of the molecular mechanisms or links of how obesity might cause an increased risk for cancer has recently been published by Khandekar et al. [31].

Efforts have been undertaken to further identify bioenergetics (i.e., food, nutrition, and physical activity) associated with overweight and obesity risk and subsequent risk of cancer as well as "tumor behavior." [8] These findings have illustrated the potential protective or promoting influences that food, nutrition, physical activity, and obesity can have upon cancer development [8]. Noting that the timeline for these influences begin with and incorporates the fetal exposure period and subsequent developmental years, careful consideration should be given to the prevention and screening of overweight and obesity among children and adolescents [34–36] in relation to their lifetime cancer risk. Estimates are that obesity among children and adolescents (defined as BMI ≥95th percentile, age and gender specific) in the United States have increased three- to sixfold [37] and suggest that 12–18 % of children and adolescents are obese [36, 38, 39]. Further, children and adolescents who are obese have a greater risk of type 2 diabetes, asthma, and nonalcoholic fatty liver disease [36, 40, 41] and are much more likely to have adult obesity, hypertension, hyperlipidemia, and metabolic syndrome [42, 43]. These data may suggest that obese children and adolescents have a greater lifetime cancer risk. For example, overweight and obesity have been associated with an earlier age onset of puberty [43], and as a result of earlier menarche, breast cancer risk may be significantly greater in adulthood [43–46]. Editors of the World Cancer Research Fund and American Institute for Cancer Research review document (2007) summarize the importance of taking the "whole life course approach" with regard to prevention of overweight and obesity [8]. They state: "Some of the most persuasive evidence in the whole field of food, nutrition, and physical activity indicates that the basis for prevention of cancer should be a whole life course approach, starting at the beginning of life, or even in maternal preparation for pregnancy." [8]

Lifestyle-Based Guidelines for Cancer Prevention

In view of the multiple studies linking obesity with increased cancer risk, one would naturally reason that individuals who are overweight or obese should be advised to reduce their body weight in order to lessen their risk for developing cancer. Following this reasoning, two specific national and international documents have provided lifestyle-related recommendations for the prevention of cancer: the *American*

Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention (American Cancer Society) [47] and *Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective* (World Cancer Fund and American Institute for Cancer Research) [8]. These two documents focus on the relevance of following a healthy diet and participating in consistent physical activity for the purpose of both preventing and treating overweight and obesity. These recommendations are in concert with prevention-oriented guidelines published by other international organizations (the European Code Against Cancer for cancer prevention [48], the American Heart Association for coronary heart disease prevention [49], and the American Diabetes Association for diabetes prevention) [50] and guidelines aimed at promoting overall good health (the 2010 *Dietary Guidelines for Americans* [51] and the 2008 *Physical Activity Guidelines for Americans*) [47, 52].

Of particular interest, the World Cancer Research Fund and the American Institute for Cancer Research has recommended that for cancer prevention, individuals should "be as lean as possible within the normal range of body weight." In addition, the guidelines identified for people who have gained weight, but remain within the normal weight range, are that they work toward returning to their original weight, and that individuals lose enough weight to approach the normal weight range if they are above the normal weight range [8]. Following an approach similar to the World Cancer Research Fund and the American Institute for Cancer Research regarding the recommendation for body weight and cancer prevention, the American Cancer Society's (ACS) guidelines encourage individuals: "Achieve and maintain weight throughout life; be as lean as possible throughout life without being underweight; and avoid excess weight gain at all ages." [47] Finally, the recommendation of the ACS for individuals who are currently overweight or obese is that they reduce body weight and keep in mind that losing even a small amount of weight is associated with health benefits. The ACS guidelines do not specifically include in their "health benefits" a reduced cancer risk, but this positive health outcome could certainly be implied. In summary, these national and international documents which contain recommendations for lifestyle intervention to prevent cancer include strong implication that individuals who participate in voluntary weight loss can reduce their risk for subsequent cancer development.

Nonsurgical Weight Loss, Cancer Prevention, and Cancer Recurrence

Although convincing evidence has linked obesity and certain cancer types, whether or not intentional weight loss reduces the risk of cancer incidence and cancer recurrence is uncertain [30, 47, 53–56]. Identified research limitations inherent in population-based studies attempting to demonstrate an association of nonsurgical weight loss and subsequent cancer risk have included the inability to maintain sustained weight loss and the limited amount of weight lost [53, 54, 56]. Although multiple studies have demonstrated short-term weight loss success when subjects engage in traditional therapy (i.e., dietary, physical activity, and behavioral interventions), the proportion of participants who achieve long-term weight loss maintenance is estimated to be as minimal as 5–10 % [56, 57]. Additional limitations of weight loss and cancer risk association studies are the failure to identify weight loss intentionality (i.e., was weight loss voluntary or not) within the reported research methods, and the absence of studies whose initial primary outcome is identified as weight loss intention [56]. For these reasons, in meaningful sized weight loss population studies with lifestyle-focused intervention (i.e., physical activity, diet and behavioral modification), successful long-term weight loss outcomes have been difficult to attain [53, 56, 57].

There are, however, a limited number of large population multicenter randomized clinical trials that have demonstrated successful weight loss through intensive lifestyle therapy and inclusion of medication. Examples of such studies are the Diabetes Prevention Program (DPP) study in which all recruited participants were prediabetic [58] and the Action for Health in Diabetes (Look AHEAD) study, where all subjects were overweight and diagnosed with type 2 diabetes [59]. Participants of the DPP who were randomized to the intensive lifestyle therapy had a 1-year reported weight loss of 7 kg (approximately 7.5 % loss from their initial weight) and gradual regain of 5 kg over the approximately next 4 years, resulting in 5-year maintenance of about 2 kg less than their initial weight [60]. Results of the Look AHEAD study, the first randomized control trial to explore whether or not weight loss, in combination with physical activity, results in a reduction of cardiovascular morbidity and mortality [61, 62], showed that participants randomized to the intensive lifestyle group had lost on average 8.6 % of their initial weight at the end of year one. At 4 years, this group had an average weight loss of 6.2 %. The intense lifestyle group also demonstrated a significant improvement in diabetes status (hemoglobin A1c level (−0.36 % versus −0.09 %; $p<0.001$)) [25].

Based upon the results of these two large population trials, the opportunity to achieve both meaningful and sustained nonsurgical weight loss appears to require intensive lifestyle intervention. Even with this in-depth therapeutic approach, the expected achieved weight loss at 1 year is 7–9 %, with weight regain after year 1. One might hypothesize that in order to sufficiently evaluate the outcome of voluntary weight loss upon subsequent cancer risk, a meaningful follow-up period (i.e., perhaps many years) coupled with a substantial degree of sustained weight loss (i.e., perhaps at least 7–10 % of initial weight) may be required. However, whether or not these weight loss criteria are essential for reducing cancer incidence and/or cancer recurrence is not

known. For example, research has demonstrated that even modest weight loss can result in improvements in insulin sensitivity, sex- and metabolic-related hormones, and inflammatory markers, all of which have been proposed to be associated with mechanisms linking obesity and cancer risk [47, 55, 63].

Keeping in mind the potential limitations of intentional weight loss and subsequent cancer risk (i.e., limited degree of weight loss, resistance to long-term weight loss maintenance, and unknown intentionality), several large population studies have explored the question of whether or not weight loss results in reduced cancer risk, cancer recurrence, and cancer mortality [20, 21, 28, 29, 64–72]. Rodriguez et al. examined BMI change (BMI self-reported in 1982 and again measured in 1992 at study enrollment) and incident prostate cancer in 69,991 men participating in the Cancer Prevention Study II Nutrition Cohort [21]. A total of 5,252 incident prostate cancers were detected through the follow-up period (from enrollment through mid-2003) [21]. Results suggested obesity increased the risk of "more aggressive prostate cancer" and "may decrease" incidence of less aggressive tumors [21]. With reference to the men who lost weight (weight loss categories were 6–10, 11–20, or ≥21 lb), the authors reported a reduction in risk of the more aggressive prostate cancer (RR 0.58, 95 % CI 0.42–0.79) [21]. In a study examining weight change (weight gain and weight loss) and cancer risk among a cohort of 64,649 Austrian adults (28,711 men; 96, 938 women), Rapp et al. reported that although the incidence of all cancers combined was not "clearly associated" with weight loss or weight gain, weight loss (>0.10 kg/m^2/year) was inversely associated with colon cancer in men (HR 0.50, 95 % CI 0.29–0.87) [64]. In a prospective study (National Institutes of Health-AARP Diet and Health Study) of adult weight change and breast cancer risk of 99,039 postmenopausal women, Ahn et al. reported that weight gain during adulthood was associated with increased breast cancer risk, but adult weight loss was "unrelated to breast cancer compared with stable weight." [65] In contrast to the study of Ahn et al., Parker and Folsom reported the results of questionnaire data regarding intentional and unintentional weight loss activity of ≥20 lb during adulthood [66]. Of the 21,707 postmenopausal women who participated, those women who "ever experienced" an intentional weight loss of ≥20 lb without a reported unintentional weight loss had an 11 % lower incidence rate for any cancer type (RR 0.89, 95 % CI 0.79–1.00) and 19 % lower for breast cancer (RR 0.81, 95 % CI 0.66–1.00), when compared with women who reported no ≥20 lb weight loss episodes [66].

The association of weight gain and weight loss (in excess of 5 % of body weight) both before and after menopause in relation to postmenopausal breast cancer risk was studied as part of the Iowa Women's Health Study [68]. A total of 33,660 postmenopausal women were followed for over 15 years, in which 1,987 incident cases of breast cancer were reported. Although study analyses were stratified by changes in weight in relation to pre- and postmenopausal time periods, the general conclusion of the results suggested that "weight loss and maintenance during these years (between age 18 years and menopause) reduces the risk of postmenopausal breast cancer." [68] Other examples of weight loss associated with subsequent cancer risk include two population-based case-control studies [67, 73]. Trentham-Dietz et al. analyzed weight change and risk of endometrial cancer in 790 newly diagnosed endometrial cases and 2,342 controls free of cancer [67]. Participants were interviewed regarding whether or not they had ever lost at least 20 lb and then gained at least half of the weight back within a 6-month period. Following adjustment for variables such as tobacco use, menopause status, and diabetes, the authors reported that women reporting a "sustained weight loss" had a reduced endometrial cancer risk (OR, 0.7; 95 % CI 0.6–0.9) [67]. As part of the Long Island Breast Cancer Study Project, Eng et al. studied 990 cases of women diagnosed with postmenopausal breast cancer compared with 1,006 controls and found that in contrast to increased postmenopausal breast cancer risk with weight gain, "weight loss over the lifetime was associated with decreased risk of postmenopausal breast cancer" (OR, 0.55; 95 % CI 0.32–0.96) [73].

More recently, review articles not specifically focused on weight loss through bariatric surgery have focused on weight loss and subsequent risk for cancer incidence and cancer recurrence risk [9, 53, 55, 56]. Wolin and Colditz reviewed the relationship between weight loss and weight gain to cancer incidence, with a specific focus on colon, breast, prostate, esophageal, pancreatic, endometrial, and kidney and renal cell cancers [53]. While their review identified multiple studies demonstrating a positive association between weight gain and some cancers, the research linking weight loss to a reduction in cancer risk was limited. With reference to weight loss and subsequent cancer risk, the authors cited studies that demonstrated reduced risk in postmenopausal breast cancer following weight loss and limited evidence linking reduced prostate cancer risk to weight loss. Further, the authors speculated that weight loss may reduce cancer adenocarcinoma of the esophagus because weight loss has been shown to lower the risk for gastroesophageal reflux, a potential partner in the mechanistic development of this cancer [53]. Wolin and Colditz emphasize that there are limited data on weight loss linked to cancer risk, likely due to "small numbers of individuals able to achieve sustained weight loss," but do conclude:If individuals achieve and maintain weight loss, we could prevent substantial cancer burden. This is most evident for postmenopausal breast cancer. The time frame for the benefits of reduced cancer risk after successful weight loss remains unclear for most cancers [53].

In a review of intentional weight loss and subsequent cancer risk, Byers and Sedjo identified three cohort studies and three dietary randomized trials where intentional weight loss was linked to a reduction in cancer risk [55]. The three cohort studies highlighted in this review have been previously dis-

cussed in this report [66, 68, 71]. While the primary design of the three dietary randomized control trial studies focused on breast cancer risk reduction (new incidence or recurrence) following dietary intervention and not on intentional weight loss [74–76], Byers and Sedjo theorized that because the dietary interventions had the potential to achieve differences in weight loss between the randomized groups, the studies could "be taken as indirect evidence about the potential impact of intentional weight loss on cancer risk." [55] In the Women's Healthy Eating and Living (WHEL) randomized trial, Pierce et al. explored the influence of a diet high in vegetables and fruit and low in fat on women who previously had been treated from early-stage breast cancer [74]. The intervention group ($n=1{,}537$) received telephone-based dietary counseling and cooking classes, and the comparison group ($n=1{,}551$) was given print material describing the 5-A-Day program. Over a mean follow-up period of 7.3 years, there were no significant differences in invasive breast cancer events or mortality between the intervention and the comparison groups. There were also no significant differences in change in body weight between groups with each group losing less than 1 kg compared with baseline [74]. The Women's Intervention Nutrition Study (WINS) included the randomization of 2,437 women with a history of breast cancer to a low-fat diet versus a control diet [76]. After a median follow-up of 60 months, the intervention group had a significantly lower dietary fat intake ($p<0.0001$) and lower body weight of approximately 6 lb compared with the control group ($p=0.005$). There was a reported 9.6 and 12.4 % decrease in breast cancer relapse events in the dietary and control groups, respectively, representing a hazard ratio in the intervention versus the control group of 0.76 (95 % CI 0.60–0.98; $p=0.077$ for stratified log rank and $p=0.34$ for adjusted Cox model analysis) [76]. From 1993 to 2005, 40 US clinical centers participated in a randomized, controlled, primary prevention study in which 48,835 postmenopausal women without prior breast cancer history were randomly assigned to a dietary intervention promoting low fat (20 %) and increased fruits and vegetables (at least five servings daily) and increased grains (at least six servings daily) or to a comparison group that were asked not to alter their dietary intake [75]. Over an 8.1-year follow-up period, 0.42 % of the intervention group and 0.45 % women of the comparison group were diagnosed with breast cancer (7 % difference), representing a hazard ratio of 0.91 (95 % CI 0.83–1.01). At 6-year follow-up, the mean difference in body weight between the intervention and comparison groups was −0.8 kg ($p<0.001$) [75]. In addition to these reported cohort and randomized control trial studies, the review by Byers and Sedjo also identified several studies designed to examine changes in cancer-related hormonal biomarkers and proinflammatory agents following intentional weight loss [55]. The authors conclude:Because both cancer incidence and levels of circulating cancer biomarkers drop fairly rapidly following weight loss, intentional weight loss may well lead to meaningful reductions in cancer risk with a short latency time [55].

An extensive and systematic review by Birks et al., published in 2012, examines the influence of weight loss upon cancer incidence and mortality [56]. Using PubMed and EMBASE, a systematic literature search was conducted for manuscripts that contained key terms such as "weight loss," "weight change," and "obesity" and were published between 1978 and April of 2011. From a total of 4,748 articles, 34 studies met that search criteria and were further analyzed. Of the 34 articles, the following categories were identified: surgical weight loss and cancer ($n=3$), intentional nonsurgical weight loss and cancer ($n=3$), any weight loss (i.e., intentionality not identified in the manuscript) and postmenopausal breast cancer ($n=10$), and any weight loss (i.e., intentionality not identified in the manuscript) and any cancer other than postmenopausal breast cancer ($n=6$ exploring all cancers and $n=12$ exploring other specific cancers) [56]. Studies identified by Birks et al. that were related to weight loss surgery will be discussed in the next section of this chapter. Of the nonsurgical weight loss surgical studies where weight loss intention was known ($n=3$), one of these studies [66] has been previously discussed. The other two reported articles were published by Williamson et al. and examined intentional weight loss and mortality in white women [77] and white men [29]. The white women-only study involved 43,457 overweight, never-smoking US participants (age range, 40–64 years) who self-reported weight, weight change information (i.e., how much weight (gain or loss), time interval and intentionality), and preexisting illnesses with specific reference to obesity-related illnesses. The vital status of participants was determined 12 years later [77]. For women who reported intentional weight losses of 1–19 lb and ≥20 lb and preexisting obesity-related illnesses, there was a significant reduction in cancer mortality risk, with an adjusted HR of 0.63 (95 % CI 0.43–0.93) and HR of 0.71 (95 % CI 0.52–0.97), respectively. Among women with intentional weight loss reported in these two weight loss ranges but without any preexisting illnesses, the cancer mortality risk varied from HR of 1.27 (95 % CI 0.98–1.65) for weight loss of 1–19 lb to HR of 0.84 (95 % CI 0.62–1.15) for weight loss ≥19 lb; neither was significant [77]. The men-only study of Williamson et al. reported no significant differences in cancer mortality risk associated with intentional weight loss [29]. Of the remaining studies reviewed by Birks et al. where weight loss intentionality was not known ($n=28$), the link between weight loss and cancer risk varied from inverse to null to positive associations [56]. As part of the discussion, Birks et al. reported:Although the literature reviewed compared cancer incidence between two equivalent groups of people (one of which achieved weight loss), only six studies (including the three [weight loss] surgery studies) investigated the effect of weight loss among specifically overweight or obese individuals. [Further] when intentional weight loss is achieved in those with excess weight,

there is consistent evidence that the incidence of cancer is reduced. When intentionality is not known, results are less clear, although more than half of such studies analyzed here still demonstrate a significant inverse association between weight loss and cancer incidence [56].

Limited research has been conducted on the use of weight loss-specific pharmacological agents and subsequent cancer risk. Given the relationship between obesity and diabetes incidence and the associated pharmacological treatment of these disorders, additional studies are likely to provide additional insight related to cancer risk following the use of drug therapy that might "target the factors thought to play a role in the cancer risk-increasing mechanisms of obesity" such as metformin [9]. In a review/meta-analysis of metformin and cancer risk in diabetic patients (11 total studies), a 31 % reduction "in overall summary relative risk" was reported to be 0.69 (95 % CI 0.61–0.79) for patients who were reported to be taking metformin compared with other antidiabetic medications [78].

Studies have suggested that increased risk of cancer recurrence may be attributed to obesity [9, 79–82]. For example, for patients who were diagnosed with cancer, a BMI in the normal range was shown to be associated with more favorable outcomes for pre- and postmenopausal women [80]. A study by Joshu et al. reported that weight gain in the period of 5 years prior to and 1 year following a prostatectomy increased the risk of prostate cancer recurrence [9, 83]. As a result of these and other similar findings, whether or not to advise overweight or obese patients recently diagnosed with cancer to voluntarily lose weight or to avoid weight gain for reasons related to reducing risk for cancer progression or recurrence is an important consideration. Unfortunately, limited data exists regarding the influence of weight loss on cancer progression or recurrence.

Bariatric Surgery, Weight Loss, and Cancer Risk

While most of the large population cancer and weight loss studies previously cited in this report have included participants who are not necessarily overweight or obese, with little exception post-bariatric surgery patients are severely obese prior to their weight loss surgery. Most insurance companies require patients seeking bariatric surgery to have first engaged in nonsurgical weight reduction activity and have a BMI of $\geq$35 kg/m^2 but <40 kg/m^2 and at least two obesity-related risk factors or a BMI $\geq$ 40 kg/m^2 [10]. The adjustable gastric banding system (Allergan©) has also been approved as a surgical treatment option for patients whose BMI is $\geq$30 kg/m^2 and who have at least one preexisting obesity-related risk factor. Following these guidelines, treatment of severe obesity through bariatric surgery has gained greater favor over the past few decades, with an estimated 344,000 weight loss surgeries performed globally in 2008 [84, 85]. Because bariatric surgery is now recognized as the only successful treatment for substantial, long-term weight loss for most severely obese patients [86–88], and due to the fact that the prevalence of extreme obesity in the United States has increased at a greater rate than moderate obesity [2, 3], the popularity of weight loss surgery is likely to continue. These trends and the resulting increase in post-bariatric surgery patients provide an ideal patient population to study the association of meaningful and sustained weight loss on subsequent cancer incidence and, in some cases, cancer recurrence.

The longest ongoing prospective bariatric surgery study is the Swedish Obesity Subjects (SOS) study, with reported significant and sustained weight loss among surgical patients for a period of greater than 10 years when compared with matched severely obese control participants [89]. Further demonstration of significant, long-term weight loss (out to 6 years) following Roux-en-Y gastric bypass surgery has been reported in the prospective Utah Obesity Study [90]. To date, three randomized clinical trials have been published comparing diabetic patients with bariatric surgical procedures or intensive medical therapy [91–93]. Although the primary outcome for each of these trials related to improved diabetes status following bariatric surgery, these studies demonstrated the successful attainment of major weight loss. Dixon et al. randomized severely obese diabetic patients to an adjustable gastric banding group or to nonsurgical medical intervention, and after two years of intervention, the surgical patients had reduced their initial body weight by 20.7 % compared with a loss of 1.7 % in the nonsurgical group [93]. Schauer et al. reported a reduction in baseline weight at 1-year intervention of 27.5 % for gastric bypass patients, 24.7 % for sleeve patients, and 5.2 % for patients receiving an intensive lifestyle-based program only [92]. At 2 years post-intervention, patients participating in the study by Mingrone et al. achieved weight loss from baseline of 33.3 %, 33.8 %, and 4.7 % for gastric bypass, biliopancreatic diversion, and the intensive lifestyle therapy program, respectively [91]. To date, associations with weight loss and subsequent cancer incidence risk have not been reported for these three trials. Results from prospective and randomized control trial studies have clearly demonstrated that significant and sustained weight loss can be achieved through bariatric surgery. The question of whether or not this intentional weight loss can impact future cancer risk can now (and has recently been) be explored using the bariatric surgery model in a manner not previously undertaken in non-weight loss population groups due to weight loss sustainability limitations of interventions previously identified in this chapter.

Likely the first study demonstrating a possible link between post-bariatric surgery weight loss and cancer mortality risk was by MacDonald et al. who prospectively followed 154 type 2 diabetic patients who underwent gastric bypass surgery and 78 severely obese type 2 diabetic patients who did not have weight loss surgery and who were matched

to the surgical patients by age, sex, and BMI [94]. The mean follow-up time was 9 years and 6.2 years for the surgical and nonsurgical groups, respectively. Although not significantly different between groups, the cancer mortality for the gastric bypass group was 0 % compared with 0.6 % cancer mortality for the nonsurgical group [94]. Since this initial paper, a number of studies have been published on the association of cancer mortality and cancer incidence risk with bariatric surgery, including review papers [25, 54–56, 84, 95–98] and prospective and retrospective studies [33, 89, 99–105].

As previously indicated, the Swedish Obesity Subjects study (SOS study) is a long-term study that has followed 2,010 patients who underwent bariatric surgery (71 % females) and 2037 severely obese participants who did not undergo weight loss surgery. Both groups were matched using multiple parameters. The study participants were followed at 25 surgical departments and 480 primary health care centers in Sweden and of the surgical group, 376 (18.7 %) underwent nonadjustable or adjustable gastric banding, 1,396 (68.1 %) had vertical banded gastroplasty, and 265 (13.2 %) Roux-en-Y gastric bypass procedures [106]. Study inclusion criteria included age between 37 and 60 years and a BMI of 34 kg/m^2 or more for men and 38 kg/m^2 for women. The initial SOS mortality study followed participants in both groups for an average of 10.9 years, and vital status was determined for all but three of the participants (follow-up rate of 99.9 %) [89].

As the SOS study is the only prospective investigation to report long-term changes in clinical variables and cancer incidence, a significant strength of this mortality study was the prospective tracking of weight. Maximum weight loss from baseline that occurred over the period of up to 15 years was 25 %, 16 %, and 14 %, respectively, for gastric bypass, vertical banded gastroplasty, and gastric banding, with an approximate ±2 % weight change among the control group [89]. The unadjusted overall total mortality HR in the surgery group when compared with the control group was 0.76 (95 % CI 0.59–0.99; $p=0.04$), and when adjusted for sex, age, and risk factors, the HR was similar at 0.71 ($p=0.01$). The SOS study reported a total of 129 deaths (6.3 %) among the control group and 101 deaths (5.0 %) in the surgical group. Interestingly, cancer was the most common cause of death over this mean 10-year period (48 deaths in the control groups compared with 29 deaths in the surgical groups), and myocardial infarction was the second leading cause of death (25 deaths among the control group and 13 deaths in the surgical group) [89].

As a follow-up study (mean follow-up of 10.9 years; range from 0 to 18.1 years) among SOS study participants, Sjöström et al., reported on the incidence of cancer [100]. The number of reported cancers among the post-bariatric surgery group was 117 compared with 169 cancers among the control group, representing an HR of 0.67 (95 % CI 0.53–0.85; $p=0.0009$). Because the SOS study consisted of primarily female participants, the female-only analysis showed the surgical group had a reported 79 cancers compared with 130 cancers in the control females, giving an HR value of 0.58 (95 % CI 0.44–0.77; $p=0.0001$). Unlike the cancer results of female-only participants, SOS reported that there were no effects related to bariatric surgery and subsequent cancer incidence in males (38 cancer cases among men in both the surgical and control groups) [100]. The lack of significant differences in cancer incidence between the male post-bariatric surgery patients and nonoperated comparison participants may have been influenced by the fewer numbers of male subjects. Exploration of possible variables associated with cancer incidence showed that the degree of weight loss or changes in energy intake among the SOS subjects participating in the bariatric surgery group were not significantly related to the reduction in cancer incidence [98]. However, sagittal trunk diameter (a substitute measure for intra-abdominal adiposity [100, 107]) was shown to contribute significantly to cancer incidence [100].

Christou et al. conducted an observational study (mean follow-up approximately 2.5 years; maximum of 5 years) of weight loss following bariatric surgery of 1,035 patients (65.6 % female; operated on between 1986 and 2002) in which bariatric surgical patients were compared with a comparison group of 5,746 age- and gender-matched severely obese patients. The comparison group was obtained from a large health care claims database (which included hospitalizations) using ICD codes that are commonly related to obesity [101]. The types of bariatric surgery included open Roux-en-Y gastric bypass (79.2 %), vertical banded gastroplasty (18.7 %) and laparoscopic Roux-en-Y gastric bypass (8 %) procedures. The mortality rate was reported as 0.68 % for the surgical group and 6.17 % for the control group [101].

As a follow-up to this initial cancer-focused study, Christou et al. published a study in which first-time physician/hospital visits were linked to eventual "all cancer diagnosis." The study population included 1,035 post-bariatric surgical patients (surgery performed between 1986 and 2002). Similar to Christou's earlier study, the age- and gender-matched morbidly obese group ($n=5,746$) of participants were identified using ICD codes for morbid obesity, who had not undergone bariatric surgery and whose data were part of a single-payer administrative database [102]. Any surgical or control participant found to have visited a physician or hospital for purposes that were related to cancer (diagnosis or treatment) within 6 months before their inclusion into the study was excluded from the analysis [54]. Analysis of the data after a maximum of 5 years follow-up showed the number of visits to the physician/hospital that led to a cancer-related diagnosis for the weight loss surgical group was 21 visits (2.0 %) compared with 487 visits (8.5 %) among the comparison group, with a relative risk of 0.22 (95 % CI 0.14–0.35; $p=0.001$) [102]. Reported relative risk for breast cancer was 0.17 (95 % CI 0.01–0.31; $p=0.001$), but menopausal status in relation to these cancers was not noted. The risk ratio for colorectal cancer between the two

groups was 0.32 (95 % CI 0.08–1.31; $p=0.63$). This study did not report all-cause mortality between study groups [54].

Drawing upon post-gastric bypass patient data collected by surgeons of the Rocky Mountain Associated Physicians (Salt Lake City, UT) over two decades, Adams et al. conducted a retrospective cohort study of long-term mortality (from 1984 to 2002) [99]. The study included 7,925 post-Roux-en-Y gastric bypass patients matched to 7,925 severely obese comparison subjects who had applied for a Utah driver's license. Matching included age, sex, BMI, and the date of bariatric surgery with the year the comparison participant applied for their driver's license. The self-reported BMI of all driver's license applicants was corrected using gender-specific regression equations derived from a subset of 592 subjects using weight that had been clinically measured before bariatric surgery. To assure that none of the comparison group participants had previously undergone weight loss surgery, they were linked to the state hospitalization registry. If a comparison participant had ICD codes for bariatric surgery, they were excluded from the study analyses [99]. Names, date of birth, Social Security numbers, and state of birth of all patients and comparison group participants were submitted to the National Death Index for the purpose of obtaining mortality status and cause of death.

Total study follow-up was 18 years with a mean follow-up of 7.1 years. For all-cause deaths, there were 213 deaths among the surgical group and 321 deaths among the group (hazard ratio of 0.60, 95 % CI 0.45–0.67; $p<0.001$, after covariate adjustment). Prevalent cancers for the surgical and comparison groups were 1.67 % and 1.59 %, respectively, not significantly different ($p=0.71$). With specific reference to cancer deaths, the gastric bypass surgery group (31 deaths; 5.5 cancer deaths per 10,000 person years) was 60 % lower than the comparison group (73 deaths; 13.3 cancer deaths per 10,000 person years) ($P=0.001$). Any cancer deaths occurring within 5 years of baseline were eliminated from the analysis [99]. Unlike the SOS study, weight and other associated clinical data at the time of death were not obtainable, and as indicated, only self-reported baseline weight was available for the comparison group participants.

Adams et al. extended the mortality follow-up study to 24 years (mean, 12.5 years) and added cancer incidence data by linking all participant data to the Utah Cancer Registry (UCR) [33]. Cancer site (type), stage, date of diagnosis, vital status, and date of death were also obtained. Subjects included gastric bypass patients who were Utah residents (6,596 of a total 9,949 post-gastric bypass patients) and severely obese comparison participants ($n=9,442$) as identified through Utah driver's license applications. There were no differences between groups for baseline cancer prevalence. Results showed that 254 (3.1/1,000 person years) and 477 (4.3/1,000 person years) incident cancers were detected in the post-gastric bypass and comparison groups, respectively [33]. For all cancers combined, the gastric bypass surgery group demonstrated a 24 % reduction in cancer incidence when compared with the comparison group (HR 0.76, 95 % CI 0.65–0.89; $p=0.0006$). Similar to other reported studies where women represent the greater percentage of bariatric surgical patients, in this study only 14 % and 17 % of the surgical and comparison participants, respectively, were men. The small number of male subjects may have influenced the finding of no significant group differences in incidence of all cancers when only males were compared. However, all incident cancers were significantly lower for females of the surgical group compared with comparison female-only group (HR 0.73, CI 0.62–0.87; $p=0.0004$). When cancers identified as "likely" to be obesity-related were grouped (esophageal adenocarcinomas, colorectal, pancreas, postmenopausal breast, corpus and uterus, kidney, non-Hodgkin lymphoma, leukemia, multiple myeloma, liver and gallbladder), incident risk for these obesity-related cancers was significantly lower in the surgery group compared with the comparison group (HR 0.62, 95 % CI 0.49–0.78), whereas the grouped "nonobesity"-related incident cancers were not significantly different between groups. Results from this study estimated that approximately 71 gastric bypass surgeries would be necessary to prevent one incident cancer [33].

When specific stratification of cancer by stage [108] at first diagnosed was performed, there were no stage differences between groups in the in situ (stage 0) and local (stage 1). However, the regional cancers (stages 2–5) were significantly lower in the surgical group compared with the comparison group (HR 0.61, 95 % CI 0.43–0.89; $p=0.009$). The distant cancers (stage 7) were also significantly lower in the surgical patients compared with comparison participants (HR 0.61, 95 % CI 0.39–0.96; $p=0.03$). Finally, the cancer case fatality rates were not significantly different between groups nor were the mean times to cancer detection [33]. As has been previously indicated, unlike the SOS study, this study only had baseline weight available, and no follow-up clinical data for surgical patients and comparison groups (other than incident cancer information) were obtained. Further discussion related to strengths and weaknesses of this study have been previously reviewed [33]. This study further surmised that:…regional and distant cancers that would have resulted without the surgery [gastric bypass] were detected in the in situ and local stages and in situ and local stage cancers that would have occurred without surgery were prevented or delayed beyond the end of the follow-up period [33].

A study by Östlund et al. addresses whether or not bariatric surgery reduces the postsurgical cancer risk to the risk of the general population [103]. Östlund et al. analyzed the incidence of obesity-related cancers among 13,123 post-bariatric surgical patients operated on in Sweden over a 26 years period (1980–2006). Cancers were identified through the Swedish Cancer Registry, and follow-up after surgery

included three different intervals: 1–4, 5–9, and ≥10 years, and the mean follow-up time was 9 years. Of the total post-bariatric surgery cohort, there were 296 obesity-related cancers identified. The number of obesity-related cancers were divided by the expected number of cancers (representing the risk at baseline and derived using the "entire background population in Sweden") to determine a standardized incidence ratio (SIR). The primary outcome for this study was the time trends for SIR.

There were no significant differences in the SIR for all obesity-related cancers combined (SIR 1.04, 95 % CI 0.93–1.17) with a p for trend of 0.40 for follow-up time [103]. However, when individual obesity-related cancers were reported, breast cancer did show a significant decrease in risk following bariatric surgery (SIR 0.55, 95 % CI 0.44–0.68) [103]. When analyzed individually, colorectal, endometrial, and kidney cancers demonstrated increased risks, with SIR values of 2.14 (95 % CI 1.33–3.22), 2.15 (95 % CI 1.62–2.81), and 2.68 (95 % CI 1.71–3.98), respectively [103]. The difference in comparison group selection between the Östlund et al. study and studies previously reviewed (i.e., using the general population versus severely obese-only subjects) presents the possibility that bariatric surgery may be associated with a reduction in obesity-related cancers when compared to nonoperated severely obese individuals, but this reduction in cancer risk, except possibly for breast cancer, may not drop to the cancer rates of the general population (whose average BMI is considerably lower than that of the severely obese and usually lower than post-bariatric surgery patients).

Reporting on the relationship of female cancers related to bariatric surgery, McCawley et al. identified women whose cancer had been diagnosed prior to their having bariatric surgery as well as women free of cancer before surgery but diagnosed with cancer following bariatric surgery [104]. Of a total of 1,482 women who underwent bariatric surgery, 34 (64.1 %) had been diagnosed prior to their surgery, with a mean interval between their cancer diagnosis and subsequent bariatric surgery of 9.9 years [104]. A total of 17 (32 %) of surgical women were diagnosed with cancer, on average, 4.2 years postsurgery [104]. Finally, one patient (1.9 %) had cancer discovered during the perioperative evaluation, and in one patient (1.9 %) the time of diagnosis was not known. McCawley et al. also included a control population of women (n = 3,495) who were severely obese. Their study results indicated that the bariatric surgical group had fewer cancers (3.6 % versus 5.8 %; p = 0.002) when compared with the severely obese comparison group [104]. However, the bariatric surgery women were significantly younger (41.7 versus 46.9 years; p < 0.001) and had cancer diagnosed as a younger age (45.0 versus 56.8 years; p < 0.001) when compared with the nonoperated group [104]. The most commonly diagnosed cancers in the bariatric surgical women were breast (n = 15, 28.3 %), endometrial (n = 9, 17 %), and cervical (n = 6, 11.3 %) cancers [104]. Although the inclusion of women whose cancer was diagnosed well before their participation in bariatric surgery makes this study design rather unique, sorting out the long-term impact of bariatric surgery-related weight loss on cancer (or cancer recurrence) may be problematic.

Gagne et al. reported on a large case series (n = 1,566; 1999–2008) of bariatric surgery patients with reference to cancer diagnosed prior to, during, or following their bariatric surgery [105]. They reported that of these patients, 36 (2.3 %), 4 (0.26 %), and 16 (0.9 %) of patients had diagnosed cancers before undergoing bariatric surgery evaluation, preoperatively, and postoperatively, respectively. In addition to this study by Gagne et al., there are multiple small case studies in the literature that report on malignancies discovered during workup for bariatric surgery, at the time of bariatric surgery, when bariatric revisional surgery is performed, and among bariatric surgical patients who at a later point in time after their bariatric surgery undergo surgery for an unrelated reason. The extent to which weight loss is related to these findings is not certain.

Concluding this section, mention is made of the increasing interest in measuring specific biomarkers in patients before and following bariatric surgery. For example, Sainsbury et al. collected mucosal biomarkers in bariatric patients (n = 26) before and 6 months after surgery and compared with mucosal biomarkers of 21 age- and sex-matched normal weight participants [109]. They reported that the mucosal biomarkers, "accepted as indictors of future colorectal cancer risk," were found to be increased in the bariatric surgical patients at 6 months after surgery when compared with the normal weight comparison group [109]. As indicated, this study was only 6 months in duration. No doubt, longer follow-up studies with greater numbers of post-bariatric surgical patients will be conducted with the intent to follow cancer-related biomarkers. Currently, however, there are a limited number of cancer biomarkers that can be included in such studies.

Exploring Potential Mechanisms Associated with Bariatric Surgery and Subsequent Cancer Risk

Highlighted in Fig. 1 is a schematic by Ashrafian et al. that presents probable physiologic mechanisms that occur following bariatric surgery and that may result in a decrease in future cancer incidence [84].

These authors suggest that bariatric (or metabolic) surgery "interrupts" the postulated mechanistic pathways that are thought to promote both obesity and subsequent cancer. As review authors, we predict that during the next few years, there will be a significant escalation in research related to the potential mechanisms postulated by Ashrafian et al., leading to a clearer understanding of the relationship of voluntary weight loss and cancer risk.

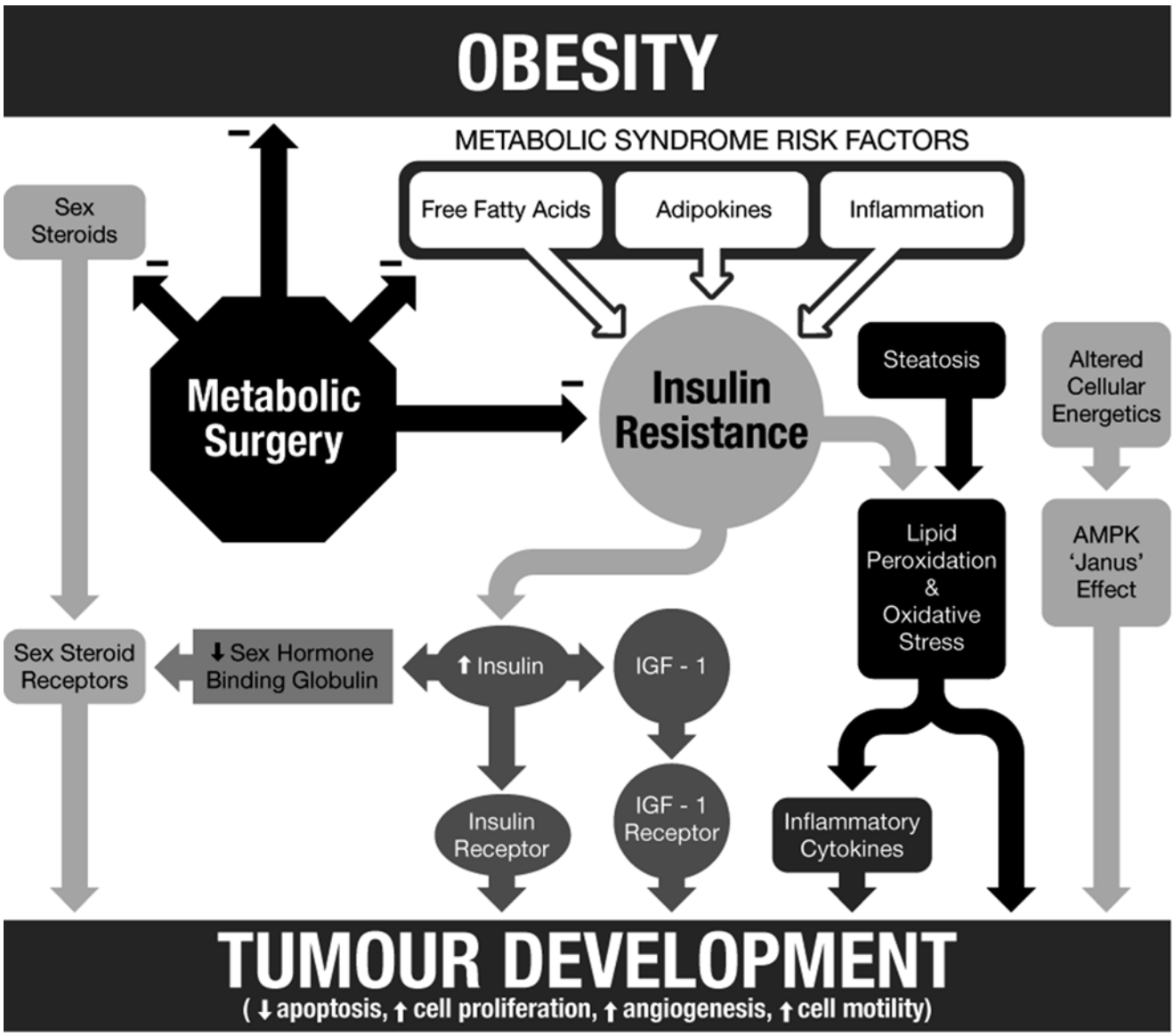

Fig. 1. Mechanisms of decreased cancer risk by metabolic surgery. IGF-1 = Insulin-like Growth Factor 1, AMPK = 5′ adenosine monophosphate-activated protein kinase. (Figure adapted from Ashrafian, et al. [84] and reprinted by permission).

Conclusion

The link between increased adiposity (i.e., obesity) and greater risk for cancer has been well established. However, due to the difficulty in achieving meaningful and sustained weight loss in large population studies, whether or not voluntary weight loss reduced the risk of cancer incidence and cancer recurrence is not entirely clear. The opportunity to study cancer risk following voluntary weight loss is possible when bariatric surgical patients are followed over time. Although limited in number, studies have demonstrated a reduction in cancer mortality among post-bariatric patients compared with severely obese, nonoperated controls. In addition, one prospective study (SOS study) and a few observational studies have shown a lower risk for cancer incidence among patients who have undergone bariatric surgery compared with nonoperated, severely obese comparison groups. One study has suggested that the risk for obesity-related cancers following bariatric surgery is not reduced below cancer rates of the background population. Further, reported reductions in obesity-related cancer risk have been limited to females, perhaps due to the greater percentage of women who undergo weight loss surgery when compared with men. With reference to the various types of bariatric surgical procedures, there is limited evidence of how these procedures might differ in relation to their potential for reducing subsequent cancer risk. There is an increasing consensus that intentional weight loss may lead to lower cancer incidence [56]. Finally, recent national and

international guidelines that have recommended weight loss for individuals (if clinically indicated), for the purpose of reducing cancer incidence risk, appear to be supported by the few weight loss and cancer studies that have been published, including those related to bariatric surgery.

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Review Questions and Answers

a. Question 1: Do pre-menopausal obese women have a greater risk for incidence of breast cancer compared to pre-menopausal normal weight women?

   Answer 1: No, population-based research suggests that pre-menopausal obese women are at lower risk for developing breast cancer compared to pre-menopausal normal weight women. However, post-menopausal obese women are at a greater risk for breast cancer compared to post-menopausal normal weight women.

b. Question 2: What are considered to be the primary mechanistic links between obesity and specific cancer types?

   Answer 2: Generally, three major categories have been identified as mechanisms associating obesity and obesity-related cancers. These include chronic inflammation, over-release of steroid-related hormones and tumor growth promotion (secondary to hyperinsulinemia.

c. Question 3: How strongly does the evidence support the recommendation that traditional weight loss reducesincident risk of cancer as well as cancer recurrence?

   Answer 3: The evidence relating weight loss from traditional therapies (i.e. diet, physical activity and behavioral modification) and reduced cancer risk are limited primarily because of the difficulty achieving significant and sustained weight loss among overweight and obese population groups.

d. Question 4: What is the evidence for reduced cancer incidence and cancer mortality among patients who have had bariatric surgery compared to obese, non-bariatric surgical subjects?

   Answer 4: Because patients who have undergone bariatric surgery generally lose a large amount of weight (i.e. greater than 20% of initial weight) and maintain significant weight loss for an extended period of time (i.e. years), these patients are ideal to study weight loss and subsequent cancer risk. There are multiple studies that have shown when bariatric cancer patients are compared to severely obese non-surgical subjects, the bariatric surgical patients demonstrate lower cancer mortality and cancer incidence when compared to severely obese non-operated controls.

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