HHS Public Access

Author manuscript

Obesity (Silver Spring). Author manuscript; available in PMC 2022 February 18.

Published in final edited form as:

Obesity (Silver Spring). 2020 September ; 28(9): 1678–1686. doi:10.1002/oby.22936.

Intensive Weight Loss Intervention and Cancer Risk in Adults with Type 2 Diabetes: Analysis of the Look AHEAD Randomized Clinical Trial

The Look AHEAD Research Group

Abstract

Objective: To determine whether intensive lifestyle intervention aimed at weight loss lowers cancer incidence and mortality.

Methods: Data from the Look AHEAD Trial were examined to investigate whether participants randomized to the intensive lifestyle intervention (ILI) designed for weight loss would have reduced overall cancer incidence, obesity-related cancer incidence, and cancer mortality, as compared to the diabetes support and education (DSE) comparison group. This analysis included 4,859 participants without a cancer diagnosis at baseline except for non-melanoma skin cancer.

Results: After a median follow-up of 11 years, 684 participants (332 in ILI and 352 in DSE) were diagnosed with cancer. The incidence rates of obesity-related cancers were 6.1 and 7.3 per 1,000 person-years in ILI and DSE, respectively, with a hazard ratio (HR) of 0.84 (95% confidence interval (CI), 0.68 to 1.04). There was no significant difference between the two groups in total cancer incidence (HR 0.93, 95% CI, 0.80 to 1.08), incidence of non-obesity related cancers (HR 1.02, 95% CI 0.83 to 1.27), or total cancer mortality (HR, 0.92, 95% CI 0.68 to 1.25).

Conclusion: An intensive lifestyle intervention aimed at weight loss lowered incidence of obesity-related cancers by 16% in adults with overweight or obesity and type 2 diabetes. The study sample size likely lacked power to determine effect sizes of this magnitude and smaller.

Keywords

Obesity; Cancer; Look AHEAD Trial

Introduction

Obesity is associated with the risk of several types of cancer (1). Based on meta-analyses or pooled analyses, relative risks range from 1.2 to 1.5 for overweight and 1.5 to 1.8 for obesity with respect to cancers of the colon (2–3), gastric cardia (4), liver (5), gallbladder

Corresponding Author: Hsin-Chieh Yeh, PhD, Associate Professor of Medicine, Epidemiology, and Oncology, Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University, 2024 E. Monument St, Suite 2-500, Baltimore, MD 21205 hyeh1@jhmi.edu.

Disclosure: Dr. Jakicic reports personal fees from WW (formerly Weight Watchers International, Inc.), outside the submitted work. No other conflicts of interest to declare.

Trial Registration: Look AHEAD Clinicaltrials.gov number, NCT00017953. https://www.clinicaltrials.gov/ct2/show/NCT00017953

(6), pancreas (7), and kidney (8). The relative risks for esophageal adenocarcinoma and endometrial cancer are even higher, up to more than 4-fold in those with BMI 40 kg/m^2 or more (9) (10). Many plausible mechanisms link obesity to cancer, including hormonal factors, circulating growth factors, and inflammation (11). While excess weight is linked to increased cancer risk, evidence is limited on whether that excess cancer risk can be reversed through intentional weight loss. In the Nurses' Health Study cohort, substantial and sustained weight loss over several years was associated with lower post-menopausal breast cancer incidence (12). The Women's Health Initiative observational cohort found intentional weight loss in postmenopausal women with obesity was associated with lower risk of obesity-related cancer, and most strongly, with a lower endometrial cancer risk (13). Data from bariatric surgery generally showed reduced cancer risks in women, but not in men (14). In the non-randomized Swedish Obese Subjects Study, women who underwent bariatric surgery experienced reduced cancer incidence compared to those who did not (15). Reduced cancer risks were also observed among female bariatric surgery patients in Utah (16) and in the Kaiser Permanente cohort (17). Still, there have been no clinical trials to date that have evaluated the effects of intensive lifestyle intervention for weight loss on the risk of incident cancer or cancer mortality.

The Look AHEAD (Action for Health in Diabetes) trial was a multi-center, randomized controlled trial of a lifestyle intervention designed to induce weight loss to reduce the risk of cardiovascular disease among individuals with overweight or obesity and type 2 diabetes. Since patients with diabetes have elevated risk for several types of cancer (18–20), Look AHEAD trial provided a unique opportunity to study cancer outcomes in a high risk population. As one of the pre-specified outcomes, we investigated whether participants randomly assigned to the intensive lifestyle intervention (ILI) had reduced cancer incidence and/or cancer mortality compared to the control group that received diabetes support and education (DSE).

METHODS

Study Population

Look AHEAD was a randomized controlled trial that recruited 5,145 individuals with overweight or obesity and type 2 diabetes from 16 study centers in the United States. Individuals were recruited from a variety of sources, including informational mailings, open screenings, advertisements and referrals from healthcare professionals (21). The design and methods of the Look AHEAD trial have been published previously (22) as well as the results for its primary cardiovascular disease (CVD) outcomes (23). The intensive lifestyle intervention produced greater reductions in weight and glycated hemoglobin, and greater initial improvements in fitness and most cardiovascular risk factors, but did not reduce the rate of cardiovascular events. After the main phase of the trial, Look AHEAD-Continuation was funded to support additional data collection, including new measures considered to be of greatest importance to an aging cohort, to continue analysis of data from the intervention phase of Look AHEAD, and to conduct close-out and additional analyses from the Look AHEAD-Continuation phase of the trial (see Study Protocol).

To be eligible, participants had to meet the following criteria: 45–76 years of age, BMI >25 kg/m^2 (>27 kg/m^2 if treated with insulin), glycated hemoglobin (HbA1c) <11% (97 mmol/mol), blood pressure <160/100 mmHg, triglyceride level <600 mg/dL, and successful completion of a maximal graded exercise test. Patients with cancer requiring treatment in the past five years, except for non-melanoma skin cancers, were not eligible for the trial. Participants were randomly assigned to an intensive lifestyle intervention (ILI) or to a diabetes support and education program (DSE). All participants provided informed consent and local institutional review boards approved the protocols. For the analysis of cancer outcomes, 4,859 trial participants who had not reported a diagnosis of cancer at baseline (except for non-melanoma skin cancer) were included (Figure 1).

Randomization

Between August 22, 2001, and April 30, 2004, patients were randomly assigned (1:1) to ILI or DSE, by a web-based data management system at the coordinating center at Wake Forest School of Medicine (Winston-Salem, NC, USA). Randomization was stratified by clinical center, with random block sizes. Allocation was concealed to study staff; the assignment was revealed only after the participant was enrolled in the clinical trial. Data were collected by trained, certified staff who were masked to the intervention. Outcomes assessors and laboratory staff were masked to treatment, but participants and interventionists were not masked because the intervention was behavioral (24).

Interventions

The intensive lifestyle intervention (ILI) was designed to achieve and maintain weight loss of at least 7% by facilitating reduced caloric intake and increased physical activity. The program included both group and individual counseling sessions, occurring weekly during the first 6 months, followed by 3 sessions per month for the second 6 months and twice-monthly contact and regular refresher group series and campaigns in years 2 to 10. Specific intervention strategies included a calorie goal of 1,200 to 1,800 kcal per day (with <30% of calories from fat and >15% from protein), the use of meal-replacement products, and at least 175 minutes of moderate-intensity physical activity per week. For the DSE comparison group, diabetes support and education was provided, featuring three group sessions per year focused on diet, exercise, and social support during years 1 through 4. In subsequent years, the frequency was reduced to one session annually. Details about the intensive lifestyle intervention and diabetes education and support program have been published elsewhere (25–26). The ILI and DSE programs were led by lifestyle counselors who were registered dieticians, behavioral counselors, or exercise specialists.

Participants in both the ILI and DSE groups were provided routine medical care by their own health care providers. The intervention began at enrollment (2001–2004) and ended in 2012 due to futility on the primary CVD outcome. The study continued after the intervention stopped; this analysis used data collected through January 2015. The mean [range] lengths of intervention for ILI and DSE participants included in the analyses for this manuscript were both 9.8 [8.4, 11.1] years.

Outcomes

At annual visits, certified staff members measured weight, height, waist circumference, and blood pressure, along with assessing medication use and obtaining blood samples for analysis at a central laboratory. During annual visits and telephone calls every 6 months, staff members queried participants about all new diagnoses, medical events, and hospitalizations. Cancer incidence was one of the pre-specified tertiary outcomes in Look AHEAD-Continuation (see Study Protocol). Cancer was listed in the study outcome form; information related to outpatient cancer care visit and cancer hospitalizations were additionally collected. Medical records were reviewed for all self-reported medical events including cancers and cancer deaths, with adjudication according to standard criteria by a central panel of physicians. For mortality, death certificates, hospital records for inpatient deaths, relevant emergency department records, and/or autopsy reports were collected. For deaths occurring as an outpatient (including pronounced dead in emergency department), an informant interview was conducted and the most recent hospital records prior to the death were reviewed. Staff obtaining and adjudicating all outcome measures were masked to study group assignment.

Cancer incidence was defined as the first reported occurrence of a malignant tumor other than non-melanoma skin cancer. Before conducting cancer-related analysis, we pre-defined obesity-related cancers based on the list published by the IARC Working Group in 2016 (18) as having sufficient evidence to be associated with high BMI and included cancers of the esophagus, colon, rectum, kidney, pancreas, uterus, ovary, post-menopausal breast, stomach cardia, liver, gallbladder, meningioma, thyroid, and multiple myeloma. Since we did not collect data on specific region of a tumor, we were not able to differentiate cancers in the gastric cardia from other stomach cancers. Similarly, biopsy reports were not always available; cancer stage and pathology were not ascertained in all cases. We were not able to differentiate esophageal adenocarcinoma from squamous cell carcinoma. There were no meningioma cases in the study.

Statistical Analysis

Analysis of the cancer outcomes was conducted on an intention-to-treat basis. Baseline characteristics were compared between the ILI and DSE groups using t-tests for continuous variables or chi-square tests for dichotomous variables. Follow-up time, in person-years, was determined for each participant using the difference in date of randomization to date of first cancer diagnosis (or cancer death for mortality analyses). Censoring dates were calculated using date of death from other causes, the last available follow-up, or the end of follow-up for this analysis (January 23, 2015).

Our primary analyses examined the effect of ILI on: 1) overall cancer incidence; 2) obesity-related cancer incidence; and 3) overall cancer mortality. Our secondary analysis considered site-specific cancer incidence. We hypothesized the impact of ILI on cancer incidence might be greater among women based on results from previous studies (3) (6); thus we additionally stratified analyses by gender and tested for a gender interaction.

Cumulative cancer incidence and cumulative cancer mortality was calculated using Kaplan-Meier estimates. Cox proportional hazards models were subsequently used to calculate hazard ratios (HRs), 95% confidence intervals (CIs), and two-sided p-values for cancer incidence and cancer mortality comparing the ILI group to the DSE group. In order to examine the heterogeneity of any possible effects on cancer incidence and cancer mortality, we conducted post-hoc analysis to test treatment-subgroup interactions for race/ethnicity, baseline BMI (<35 vs. >=35 based on the median), smoking status (ever vs never), and age (<58 vs. >=58 based on the median). Proportional hazards assumptions were verified for each model and results were not adjusted for multiple comparisons. A sensitivity analysis on overall cancer incidence and obesity-related cancer incidence were conducted using the Fine and Gray method. A p-value less than 0.05 was considered to indicate statistical significance. All analyses were performed using SAS version 9.4 (Cary, NC).

RESULTS

Baseline characteristics are shown in Table 1 by intervention assignment. Characteristics of the participants included in this analysis did not differ by randomization assignment, except for small differences in systolic and diastolic blood pressure, HbA1c, and family history of diabetes. The distribution of variables in this study population was similar to that in the original Look AHEAD cohort (11). Baseline characteristics by sex and by study arm are shown in Table S1 (see Supplementary Results).

Participants in the ILI group had significantly greater reductions in weight than those in the DSE group (Figure S1 in Supplementary Results). Differences in mean weight loss (expressed as kg and percentage) were largest at 1 year (8.73 ± 7.54 kg (8.6% ± 6.8%) in the ILI group vs. 0.75 ± 5.00 kg (0.7% ± 4.8%) in the DSE group) but remained significant throughout the trial. After 12 years of follow-up, the mean weight loss from baseline was 6.84 ± 10.96 kg (6.5% ± 9.9%) in the ILI group and 4.87 ± 12.28 kg (4.6% ± 11.5%) in the DSE group.

During a median follow up of 11 years, 684 participants developed cancer of any type (332 in the ILI group and 352 in the DSE group; Figure 2a), with corresponding overall cancer incidence rates of 13.2 and 14.2 per 1,000 person-years, respectively (HR 0.93, 95% CI, 0.80 to 1.08) (Table 2). The incidence rates of obesity-related cancers were 6.1 and 7.3 per 1,000 person-years in ILI and DSE, respectively, with hazard ratio of 0.84 (95% CI, 0.68 to 1.04.). There was no difference for cancers not related to obesity (HR 1.02, 95% CI 0.83 to 1.27). The Kaplan-Meier survival curves show that the incidence of obesity-related cancers in the intervention group was lower throughout the follow-up period, but the difference between two groups did not achieve statistical significance (Figure 2b). The intervention effect on obesity-related cancer incidence did not differ between men and women (p= 0.68 for interaction). The corresponding hazard ratios stratified by sex were 0.78 (95% CI, 0.51 to 1.19) and 0.86 (95% CI, 0.67 to1.10) in men and women, respectively. A total of 80 participants in the ILI group and 85 in the DSE group died of cancer during follow-up (Figure 2c), corresponding to cancer mortality rates of 3.0 and 3.2 per 1,000 person-years, respectively (HR= 0.92, 95% CI, 0.68 to 1.25) (Table 3).

Post-hoc analyses to test treatment-subgroup interaction for race/ethnicity, baseline age, BMI, and smoking status were conducted to examine the heterogeneity of any possible effects on overall cancer incidence, obesity-related cancer incidence, and cancer mortality. None of the interactions was statistically significant. Figure 3 showed results from subgroup analysis of obesity-related cancer incidence.

Results from site-specific analyses were shown in Supplementary Results (Table S2–S7). Moreover, in the sensitivity analysis incorporating competing risk from death for overall cancer incidence and obesity-related cancer incidence, the results were almost identical.

DISCUSSION

We compared the cancer incidence and mortality of individuals with overweight or obesity and type 2 diabetes who were randomly assigned to a 10-year intensive lifestyle intervention (ILI) designed for weight loss with those assigned to a control regimen of diabetes support and education (DSE). After a median follow-up of 11 years, the intensive lifestyle intervention was not associated with significant reduction in overall cancer incidence or cancer mortality, likely due to insufficient power for either outcome. We found that the intensive lifestyle intervention lowered incidence of obesity-related cancers (HR=0.84, 95% CI, 0.58 to 1.04). The relatively small number of cancer cases likely increased the 95% confidence intervals to include 1. Since we did not collect data on specific region of a tumor (e.g. cardia of stomach, esophageal adenocarcinoma) where associations are very strong with obesity), the misclassification may lead to under-estimating the intervention effect.

Obesity is associated with metabolic and endocrine disruptions, which include alterations in sex hormone metabolism, insulin and insulin-like growth factor signaling, and inflammatory pathways (27–29). Weight loss decreases intra-abdominal fat and the levels of the endogenous insulins sensitizer adiponectin which, in turn, improves insulin, pro-inflammatory cytokines, and may lead to lower cell proliferation and a lower likelihood to develop cancers (30–31). Evidence from clinical trials in overweight or obese postmenopausal women demonstrated weight loss through caloric restriction diet with or without exercise resulted in favorable effects on serum sex hormone (32 and 33), improved insulin resistance (34), reduced inflammatory biomarkers (35, 36), oxidative stress (37), and angiogenesis (38). These underlying mechanisms provided molecular and endocrine evidence supporting the hypothesis that weight loss may reduce the risk of obesity-related cancers.

Epidemiological studies also suggested that intentional weight loss positively affects these mechanisms (2) as well as reduces cancer risk. The Nurses' Health Study, which included a total of 87,143 postmenopausal women followed up for up to 24 years, found women who had lost 10 kg or more since menopause and had never used postmenopausal hormones were at a lower risk of breast cancer than those who did not lose weight (RR, 0.43; 95% CI, 0.21–0.86; P = 0.01) (3). In our study, women randomized to the weight loss intervention had a 22% reduced risk of postmenopausal breast cancer, but the association was not statistically significant (HR, 0.78; 95% CI, 0.56, 1.09). Compared to the Nurses' Health Study, our study had far fewer cases and the average amount of weight loss was about 6 kg in the

intervention group, compared to ≥10 kg observed in the NHS showing reduced cancer risk. The relative moderate weight loss in the ILI arm may not be enough to mitigate cancer risks. Nonetheless, the subset of those losing ≥10 kg in the Nurses' Health Study in the absence of a study intervention are not comparable to participants in the intervention group of a randomized clinical trial.

The Women's Health Initiative (WHI) observational study, which included 58,667 postmenopausal women with 12 years of follow-up, found that when compared with women who were weight stable (±5%), those who lost ≥5% had a significantly lower obesity-related cancer risk (HR, 0.88; 95% CI, 0.80 to 0.98) (13). This magnitude was similar to the effect size observed in our study.

The Swedish Obese Subjects (SOS) study involved 2,010 patients with obesity (BMI ≥34 kg/m^2 in men and ≥38 kg/m^2 in women) who underwent bariatric surgery and 2,037 matched controls, but treatment was not assigned at random, complicating analyses of outcomes among those who did or did not undergo surgery. Over 10 years, compared to the control group, the incidence rate of cancer was 33% lower in the surgery group (HR 0.67, 95% CI 0.53–0.85). However, the reduced risk of cancer was seen only in women (HR 0.58, 95% CI 0.44–0.77), but not in men (HR 0.97, 95% CI 0.62–1.52) (6). Cancer risk was reduced in some obesity-related cancer sites including ovary, colorectal, breast, and endometrial, but site-specific numbers were small and the site-specific differences were not statistically significant. Unlike the SOS Study, our trial did not observe a significant sex-intervention interaction on obesity-related cancer. In a study that included 6,596 Utah patients who had gastric bypass and 9,442 controls who were matched with surgery patients by sex, age, and BMI categories (7), obesity-related cancer incidence (HR=0.62, 95% CI, 0.49 to 0.78) and cancer mortality (HR = 0.54; 95% CI, 0.32–0.90) were significantly lower in the surgical group compared to controls after a mean of 12.5-years of follow-up. The large reductions may be partly due to unaccounted residual confounders since the surgery group had better education, socioeconomic status, access to care, and health at baseline than the controls. Even though meta-analysis(5) showed patients undergoing bariatric surgery had reduced cancer risk, the number and quality of these studies were insufficient for conclusions. Furthermore, the Look AHEAD participants were older at baseline (average 58 years) than patients included in bariatric surgery studies. Our findings pose the unanswered question of whether intentional weight loss should be provided earlier in life to achieve significant benefit on cancer prevention.

The World Cancer Research Fund has estimated that in the United States, excess adiposity accounts for about 17% of the risk for postmenopausal breast cancer, 15–17% for colorectal cancer, 20–28% for kidney cancer, and 17–20% for pancreatic cancer(39). The risk reduction observed in the Look AHEAD Trial, though non-significant, is of a similar magnitude as would be expected if most of the excess cancer risk imparted by obesity were reversible with moderate amounts of intentional weight loss. Indeed, lifestyle intervention achieved a smaller magnitude of intentional weight loss as compared to bariatric surgery, but the non-invasive, public health approach is meaningful at the population level. In addition, the hypothesis of greater effect of the ILI in prevention of obesity-related cancers as a group

than other cancers was observed. Additional cancer outcomes could accrue with a longer follow-up in Look AHEAD participants.

Many studies have supported an association between increased BMI near the time of cancer diagnosis and reduced survival in patients with breast cancer (40), whereas evidence for other cancers has been limited. Large-scale, ongoing clinical trials of weight loss in breast cancer survivors, such as the Breast Cancer Weight Loss (BWEL) study (41), will shed light on the impact of weight loss on breast cancer recurrence and survival.

Studies have suggested that certain glucose-lowering medications, including metformin, thiazolidinediones, insulin, and incretin-based therapies, are associated with decreased or increased risk of cancer. Data from randomized clinical trials are very scant due to relatively short follow-up times in trial settings. Results from observational studies have been heterogeneous; many studies suffered from biases, particularly time-related biases and confounding by indication (42). In addition, most patients with diabetes, like participants in the Look AHEAD Trial, were treated with one or more medications, making it difficult to assess independent associations of individual medication. Continuous monitoring of the cancer issues related to anti-diabetes medications are still required.

To our knowledge, this study is the only randomized clinical trial that has examined long-term cancer outcomes in an intensive lifestyle intervention focused on weight loss. Cancer outcomes were pre-specified and underwent careful adjudication. Nonetheless, there are several limitations. The Look AHEAD trial was limited to adults with type 2 diabetes and high BMI at baseline. Whether these findings can be generalized to all adults with excess adiposity is not known. Another limitation of the Look AHEAD trial was the insufficient number of many site-specific cancers, which generated site-specific results that must be viewed with caution. We did not have complete information on cancer stage at diagnosis, which limited the opportunity to investigate if the intervention was associated with a differential stage of cancer. Pooled-data from weight loss trials with long-term follow-up will be useful in assessing the effect of weight loss on cancer risk. To that end, future long-term trials of weight loss should include obesity-related cancers as a pre-specified end-point for adjudication. Finally, participants in the DSE comparison group also received some intervention and lost weight over the study period, which may reduce obesity-related cancer risks and explain some of the non-significant results.

This study showed that an intensive lifestyle intervention aimed at weight loss lowered incidence of obesity-related cancers by 16% in adults with overweight or obesity and type 2 diabetes. Although the result was not statistically significant, this finding provided evidence that patients with obesity can reduce their cancer risk through weight loss.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding Sources:

Funded by the National Institutes of Health through cooperative agreements with the National Institute of Diabetes and Digestive and Kidney Diseases: DK57136, DK57149, DK56990, DK57177, DK57171, DK57151, DK57182, DK57131, DK57002, DK57078, DK57154, DK57178, DK57219, DK57008, DK57135, and DK56992. Additional funding was provided by the National Heart, Lung, and Blood Institute; National Institute of Nursing Research; National Center on Minority Health and Health Disparities; NIH Office of Research on Women's Health; and the Centers for Disease Control and Prevention. This research was supported in part by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases. The Indian Health Service (I.H.S.) provided personnel, medical oversight, and use of facilities. The opinions expressed in this paper are those of the authors and do not necessarily reflect the views of the I.H.S. or other funding sources. Additional support was received from The Johns Hopkins Medical Institutions Bayview General Clinical Research Center (M01RR02719); the Massachusetts General Hospital Mallinckrodt General Clinical Research Center and the Massachusetts Institute of Technology General Clinical Research Center (M01RR01066); the Harvard Clinical and Translational Science Center (RR025758-04); the University of Colorado Health Sciences Center General Clinical Research Center (M01RR00051) and Clinical Nutrition Research Unit (P30 DK48520); the University of Tennessee at Memphis General Clinical Research Center (M01RR0021140); the University of Pittsburgh General Clinical Research Center (GCRC) (M01RR000056), the Clinical Translational Research Center (CTRC) funded by the Clinical & Translational Science Award (UL1 RR 024153) and NIH grant (DK 046204); the VA Puget Sound Health Care System Medical Research Service, Department of Veterans Affairs; and the Frederic C. Bartter General Clinical Research Center (M01RR01346). The following organizations have committed to make major contributions to Look AHEAD: FedEx Corporation; Health Management Resources; LifeScan, Inc., a Johnson & Johnson Company; OPTIFAST® of Nestle HealthCare Nutrition, Inc.; Hoffmann-La Roche Inc.; Abbott Nutrition; and Slim-Fast Brand of Unilever North America. Some of the information contained herein was derived from data provided by the Bureau of Vital Statistics, New York City Department of Health and Mental Hygiene.

Appendix

Writing group members: Hsin-Chieh Yeh, PhD (Chair), Christos Mantzoros, MD, DSc, Mara Vitolins, DrPH, Rebecca Sedjo, PhD, Lynne Wagenknecht, DrPH, Jeanne M. Clark, MD, MPH, Katelyn Garcia, MS, Antonio Wolff, MD, Edward Horton, MD, George Blackburn, MD, PhD (deceased), Tim Byers, MD, MPH.

A di-identified database will be prepared and submitted to the NIDDK Central Repository. Included will be documentation including protocols, forms, and data dictionaries. Access is guided by NIDDK Central Repository policy.

Authors:

Hsin-Chieh Yeh, PhD

John P. Bantle, MD

Maria Cassidy-Begay, BSND, RND

George Blackburn+, MD, PhD

George A. Bray, MD

Tim Byers, MD, MPH

Jeanne M. Clark, MD, MPH

Mace Coday, PhD

Caitlin Egan, MS

Mark A. Espeland, PhD

John P. Foreyt, PhD

Katelyn Garcia, MS

Valerie Goldman, MS, RD

Edward W. Gregg, PhD

Helen P. Hazuda, PhD

Louise Hesson, MSN, CRNP

James O. Hill, PhD

Edward S. Horton, MD

John M. Jakicic, PhD

Robert W. Jeffery, PhD

Karen C. Johnson, MD, MPH

Steven E. Kahn, MB, ChB

William C. Knowler, MD, DrPH

Mary Korytkowski, MD

Anne Kure, BS

Cora E. Lewis, MD, MSPH

Christos Mantzoros, MD, DSc

Maria Meacham, BSN, RN, CDE

Maria G. Montez, RN, MSHP, CDE

David M. Nathan, MD

Nicholas Pajewski, PhD

Jennifer Patricio, MS

Anne Peters, MD

F. Xavier Pi-Sunyer, MD

Henry Pownall, PhD

Donna H. Ryan, MD

Monika Safford, MD

Rebecca L. Sedjo, PhD

Helmut Steinburg, MD

Mara Vitolins, DrPH

Thomas A. Wadden, PhD

Lynne E. Wagenknecht, DrPH

Rena R. Wing, PhD

Antonio C. Wolff, MD

Holly Wyatt, MD

Susan Z. Yanovski, MD

Bibliography

1. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K, et al. Body Fatness and Cancer--Viewpoint of the IARC Working Group. The New England journal of medicine. 2016 Aug 25;375(8):794–8. [PubMed: 27557308]
2. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008 Feb 16;371(9612):569–78. doi: 10.1016/S0140-6736(08)60269-X. [PubMed: 18280327]
3. Ma Y, Yang Y, Wang F, Zhang P, Shi C, Zou Y, Qin H. Obesity and risk of colorectal cancer: a systematic review of prospective studies. PLoS One. 2013;8(1):e53916. doi: 10.1371/journal.pone.0053916. [PubMed: 23349764]
4. Chen Y, Liu L, Wang X, Wang J, Yan Z, Cheng J, Gong G, Li G. Body mass index and risk of gastric cancer: a meta-analysis of a population with more than ten million from 24 prospective studies. Cancer Epidemiol Biomarkers Prev. 2013 Aug;22(8):1395–408. doi: 10.1158/1055-9965.EPI-13-0042. [PubMed: 23697611]
5. Chen Y, Wang X, Wang J, Yan Z, Luo J. Excess body weight and the risk of primary liver cancer: an updated meta-analysis of prospective studies. Eur J Cancer. 2012 Sep;48(14):2137–45. doi: 10.1016/j.ejca.2012.02.063. [PubMed: 22446023]
6. World Cancer Research Fund International. Continuous Update Project: diet, nutrition, physical activity and gallbladder cancer. 2015 (http://www.wcrf.org/sites/default/files/Gallbladder-Cancer-2015-Report.pdf).
7. Genkinger JM, Spiegelman D, Anderson KE, Bernstein L, van den Brandt PA, Calle EE, English DR, Folsom AR, Freudenheim JL, Fuchs CS, Giles GG, Giovannucci E, Horn-Ross PL, Larsson SC, Leitzmann M, Männistö S, Marshall JR, Miller AB, Patel AV, Rohan TE, Stolzenberg-Solomon RZ, Verhage BA, Virtamo J, Willcox BJ, Wolk A, Ziegler RG, Smith-Warner SA. A pooled analysis of 14 cohort studies of anthropometric factors and pancreatic cancer risk. Int J Cancer. 2011 Oct 1;129(7):1708–17. doi: 10.1002/ijc.25794. [PubMed: 21105029]
8. Wang F, Xu Y. Body mass index and risk of renal cell cancer: a dose-response meta-analysis of published cohort studies. Int J Cancer. 2014 Oct 1;135(7):1673–86. doi: 10.1002/ijc.28813. [PubMed: 24615287]

9. Hoyo C, Cook MB, Kamangar F, Freedman ND, Whiteman DC, Bernstein L, Brown LM, Risch HA, Ye W, Sharp L, Wu AH, Ward MH, Casson AG, Murray LJ, Corley DA, Nyrén O, Pandeya N, Vaughan TL, Chow WH, Gammon MD. Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the International BEACON Consortium. Int J Epidemiol. 2012 Dec;41(6):1706–18. doi: 10.1093/ije/dys176. [PubMed: 23148106]
10. Crosbie EJ, Zwahlen M, Kitchener HC, Egger M, Renehan AG. Body mass index, hormone replacement therapy, and endometrial cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2010 Dec;19(12):3119–30. doi: 10.1158/1055-9965.EPI-10-0832. [PubMed: 21030602]
11. Byers T, Sedjo RL. Does intentional weight loss reduce cancer risk? Diabetes, obesity & metabolism. 2011 Dec;13(12):1063–72.
12. Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. JAMA : the journal of the American Medical Association. 2006 Jul 12;296(2):193–201. [PubMed: 16835425]
13. Luo J, Hendryx M, Manson JE, Figueiredo JC, LeBlanc ES, Barrington W, Rohan TE, Howard BV, Reding K, Ho GY, Garcia DO, Chlebowski RT. Intentional Weight Loss and Obesity-Related Cancer Risk. JNCI Cancer Spectr. 2019 Aug 9;3(4):pkz054. doi:10.1093/jncics/pkz054. [PubMed: 31737862]
14. Tee MC, Cao Y, Warnock GL, Hu FB, Chavarro JE. Effect of bariatric surgery on oncologic outcomes: a systematic review and meta-analysis. Surgical endoscopy. 2013 Dec;27(12):4449–56. [PubMed: 23949484]
15. Sjostrom L, Gummesson A, Sjostrom CD, Narbro K, Peltonen M, Wedel H, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. The lancet oncology. 2009 Jul;10(7):653–62. [PubMed: 19556163]
16. Adams TD, Stroup AM, Gress RE, Adams KF, Calle EE, Smith SC, et al. Cancer incidence and mortality after gastric bypass surgery. Obesity. 2009 Apr;17(4):796–802. [PubMed: 19148123]
17. Schauer DP, Feigelson HS, Koebnick C, Caan B, Weinmann S, Leonard AC, et al. Bariatric Surgery and the Risk of Cancer in a Large Multisite Cohort. Annals of surgery. 2017 Sep 21.
18. Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol. 2004 Jun 15;159(12):1160–7. [PubMed: 15191933]
19. Tsilidis KK, Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JP. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. BMJ. 2015 Jan 2;350:g7607. doi: 10.1136/bmj.g7607. [PubMed: 25555821]
20. Yeh HC, Platz EA, Wang NY, Visvanathan K, Helzlsouer KJ, Brancati FL. A prospective study of the associations between treated diabetes and cancer outcomes. Diabetes Care. 2012 Jan;35(1):113–8. doi: 10.2337/dc11-0255. [PubMed: 22100961]
21. Look AHEAD Research Group. Bray G, Gregg E, Haffner S, Pi-Sunyer XF, WagenKnecht LE, et al. Baseline characteristics of the randomised cohort from the Look AHEAD (Action for Health in Diabetes) study. Diabetes & vascular disease research : official journal of the International Society of Diabetes and Vascular Disease. 2006 Dec;3(3):202–15.
22. Ryan DH, Espeland MA, Foster GD, Haffner SM, Hubbard VS, Johnson KC, et al. Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. Controlled clinical trials. 2003 Oct;24(5):610–28. [PubMed: 14500058]
23. Look AHEAD Research Group. Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. The New England journal of medicine. 2013 Jul 11;369(2):145–54. [PubMed: 23796131]
24. Look AHEAD Research Group. Effect of a long-term behavioural weight loss intervention on nephropathy in overweight or obese adults with type 2 diabetes: a secondary analysis of the Look AHEAD randomised clinical trial. The lancet Diabetes & endocrinology. 2014 Oct;2(10):801–9. [PubMed: 25127483]

25. Look AHEAD Research Group, Wadden TA, West DS, Delahanty L, Jakicic J, Rejeski J, et al. The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. Obesity. 2006 May;14(5):737–52. [PubMed: 16855180]

26. Wesche-Thobaben JA. The development and description of the comparison group in the Look AHEAD trial. Clinical trials. 2011 Jun;8(3):320–9. [PubMed: 21730080]

27. Arnold M, Pandeya N, Byrnes G, Renehan AG, Stevens GA, Ezzati M, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. The lancet oncology. 2014 Nov 26.

28. Hursting SD, Digiovanni J, Dannenberg AJ, Azrad M, Leroith D, Demark-Wahnefried W, et al. Obesity, energy balance, and cancer: new opportunities for prevention. Cancer prevention research. 2012 Nov;5(11):1260–72. [PubMed: 23034147]

29. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nature reviews Cancer. 2004 Aug;4(8):579–91. [PubMed: 15286738]

30. Moschos SJ, Mantzoros CS. The role of the IGF system in cancer: from basic to clinical studies and clinical applications. Oncology. 2002;63(4):317–32. [PubMed: 12417786]

31. Boutari C, Mantzoros CS. Inflammation: A key player linking obesity with malignancies. Metabolism: clinical and experimental. 2018 Apr;81:A3–A6. [PubMed: 29309747]

32. Campbell KL, Foster-Schubert KE, Alfano CM, Wang CC, Wang CY, Duggan CR, Mason C, Imayama I, Kong A, Xiao L, Bain CE, Blackburn GL, Stanczyk FZ, McTiernan A. Reduced-calorie dietary weight loss, exercise, and sex hormones in postmenopausal women: randomized controlled trial. J Clin Oncol. 2012 Jul 1;30(19):2314–26. doi: 10.1200/JCO.2011.37.9792.

33. van Gemert WA, Schuit AJ, van der Palen J, May AM, Iestra JA, Wittink H, Peeters PH, Monninkhof EM. Effect of weight loss, with or without exercise, on body composition and sex hormones in postmenopausal women: the SHAPE-2 trial. Breast Cancer Res. 2015 Sep 2;17:120. doi: 10.1186/s13058-015-0633-9. [PubMed: 26330303]

34. Mason C, Foster-Schubert KE, Imayama I, Kong A, Xiao L, Bain C, Campbell KL, Wang CY, Duggan CR, Ulrich CM, Alfano CM, Blackburn GL, McTiernan A. Dietary weight loss and exercise effects on insulin resistance in postmenopausal women. Am J Prev Med. 2011 Oct;41(4):366–75. doi: 10.1016/j.amepre.2011.06.042. [PubMed: 21961463]

35. Imayama I, Ulrich CM, Alfano CM, Wang C, Xiao L, Wener MH, Campbell KL, Duggan C, Foster-Schubert KE, Kong A, Mason CE, Wang CY, Blackburn GL, Bain CE, Thompson HJ, McTiernan A. Effects of a caloric restriction weight loss diet and exercise on inflammatory biomarkers in overweight/obese postmenopausal women: a randomized controlled trial. Cancer Res. 2012 May 1;72(9):2314–26. doi: 10.1158/0008-5472.CAN-11-3092. [PubMed: 22549948]

36. van Gemert WA, May AM, Schuit AJ, Oosterhof BY, Peeters PH, Monninkhof EM. Effect of Weight Loss with or without Exercise on Inflammatory Markers and Adipokines in Postmenopausal Women: The SHAPE-2 Trial, A Randomized Controlled Trial. Cancer Epidemiol Biomarkers Prev. 2016 May;25(5):799–806. doi: 10.1158/1055-9965.EPI-15-1065. Epub [PubMed: 26908432]

37. Duggan C, Tapsoba JD, Wang CY, Campbell KL, Foster-Schubert K, Gross MD, McTiernan A. Dietary Weight Loss, Exercise, and Oxidative Stress in Postmenopausal Women: A Randomized Controlled Trial. Cancer Prev Res (Phila). 2016 Nov;9(11):835–843. [PubMed: 27803047]

38. Duggan C, Tapsoba Jde D, Wang CY, McTiernan A. Dietary Weight Loss and Exercise Effects on Serum Biomarkers of Angiogenesis in Overweight Postmenopausal Women: A Randomized Controlled Trial. Cancer Res. 2016 Jul 15;76(14):4226–35. doi: 10.1158/0008-5472.CAN-16-0399. [PubMed: 27417562]

39. World Cancer Researcg Fund. Cancer preventability estimates for body fatness [cited 2020 April 7, 2020]. Available from: http://www.wcrf.org/int/cancer-facts-figures/preventability-estimates/cancer-preventability-estimates-body-fatness.

40. Jiralerspong S, Goodwin PJ. Obesity and Breast Cancer Prognosis: Evidence, Challenges, and Opportunities. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2016 Dec 10;34(35):4203–16. [PubMed: 27903149]

41. Ligibel JA, Barry WT, Alfano C, Hershman DL, Irwin M, Neuhouser M, et al. Randomized phase III trial evaluating the role of weight loss in adjuvant treatment of overweight and obese

women with early breast cancer (Alliance A011401): study design. NPJ breast cancer. 2017;3:37. [PubMed: 28948213]

42. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. Diabetes care. 2012 Dec;35(12):2665–73. [PubMed: 23173135]

Study Importance

- Observational studies show clear associations between obesity and risk of some cancers, but there have been no clinical trials to date that have evaluated the effects of intensive lifestyle intervention for weight loss on the risk of incident cancer or cancer mortality.
- Data from the Look AHEAD Trial indicated an intensive lifestyle intervention aimed at weight loss lowered incidence of obesity-related cancers by 16% in adults with overweight or obesity and type 2 diabetes. The 95% confidence interval did cross 1.0, but that was likely due to the insufficient sample size.
- Future trials need to be adequately powered to test weight loss effects on risk of specific obesity-related individual cancers.

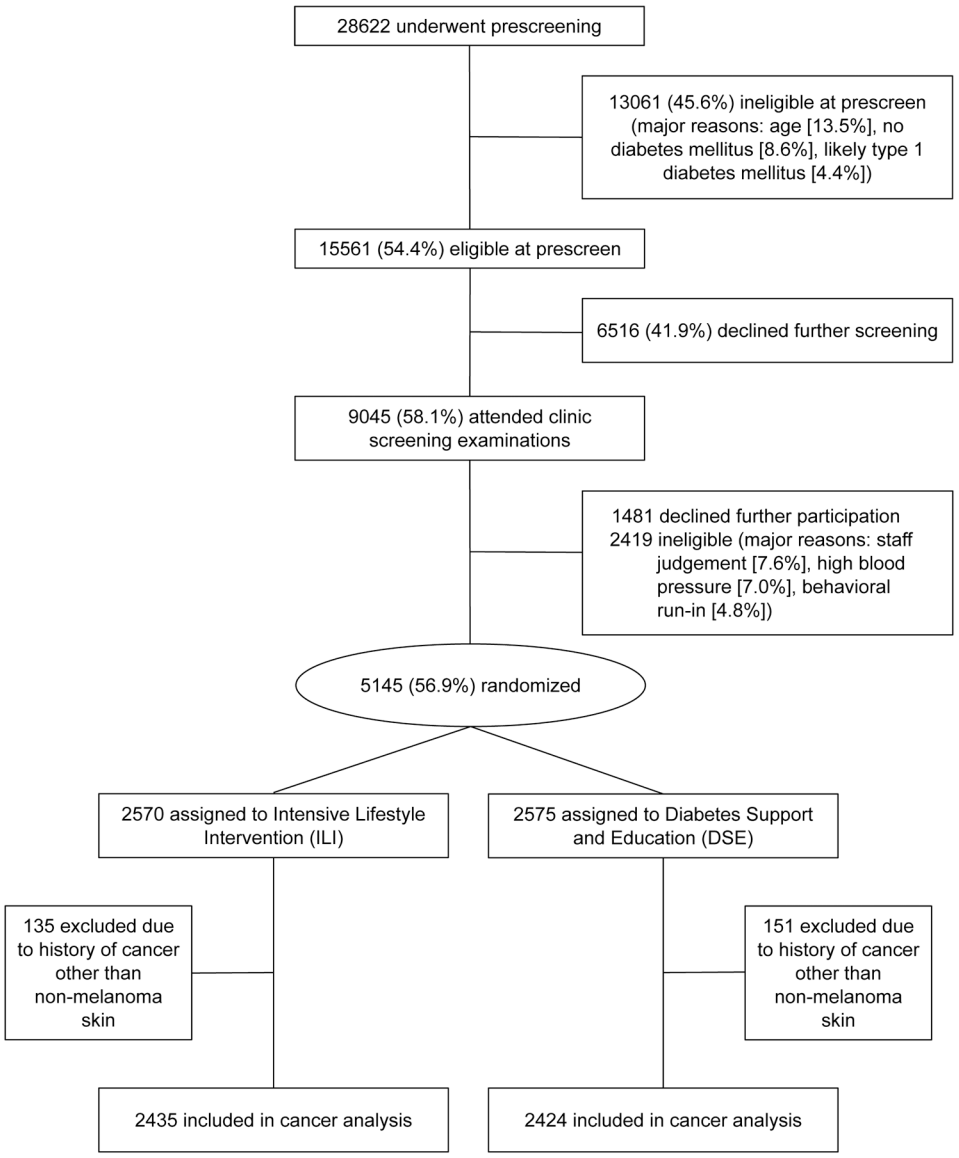

Figure 1:
Flowchart for screening, randomization, and cancer analysis

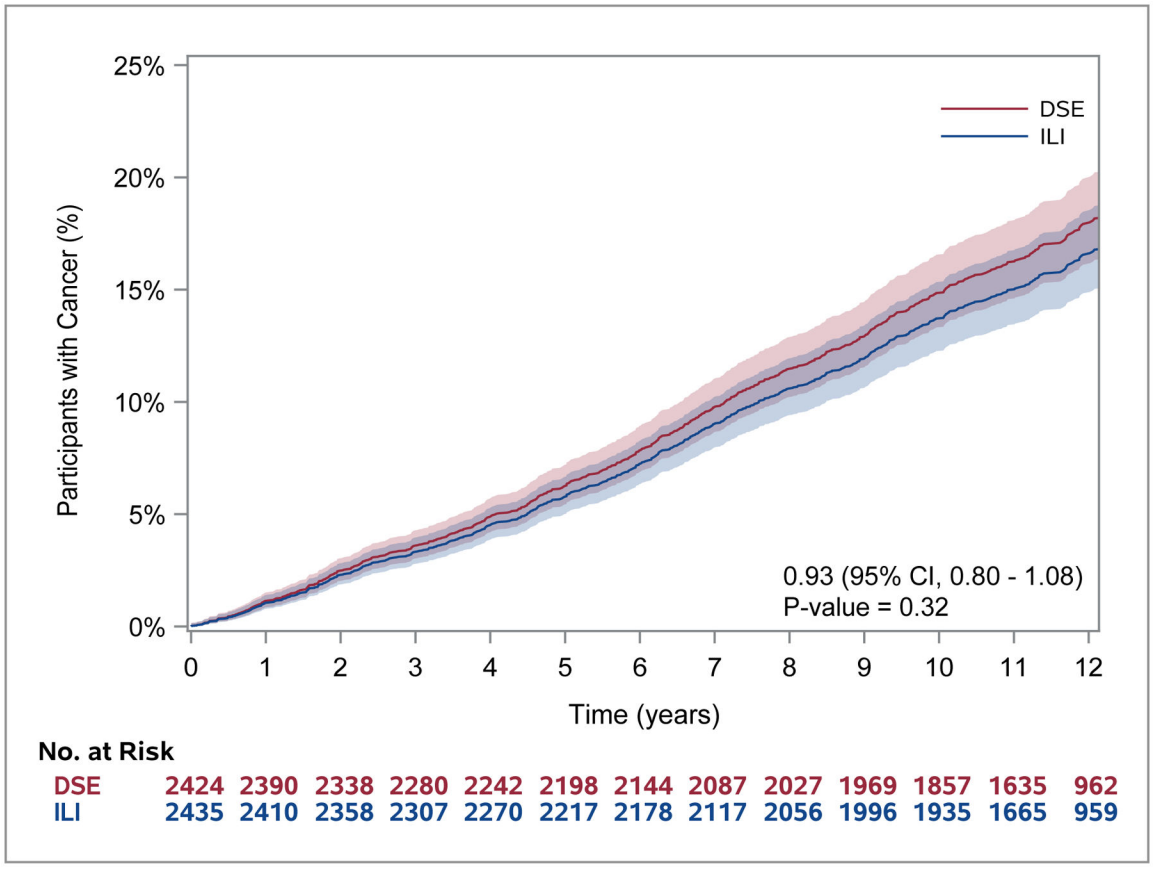

Figure 2a:
Cumulative incidence of all cancers

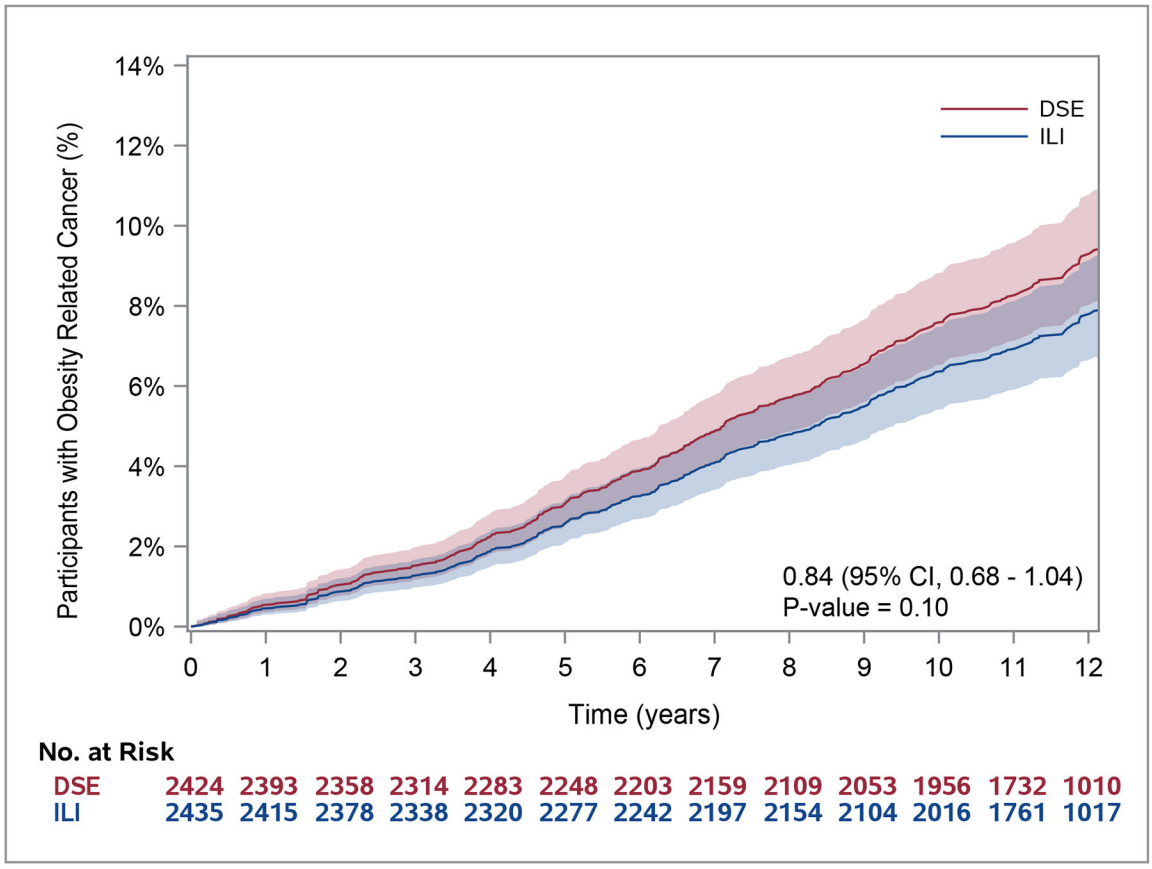

Figure 2b:
Cumulative incidence of obesity-related cancers

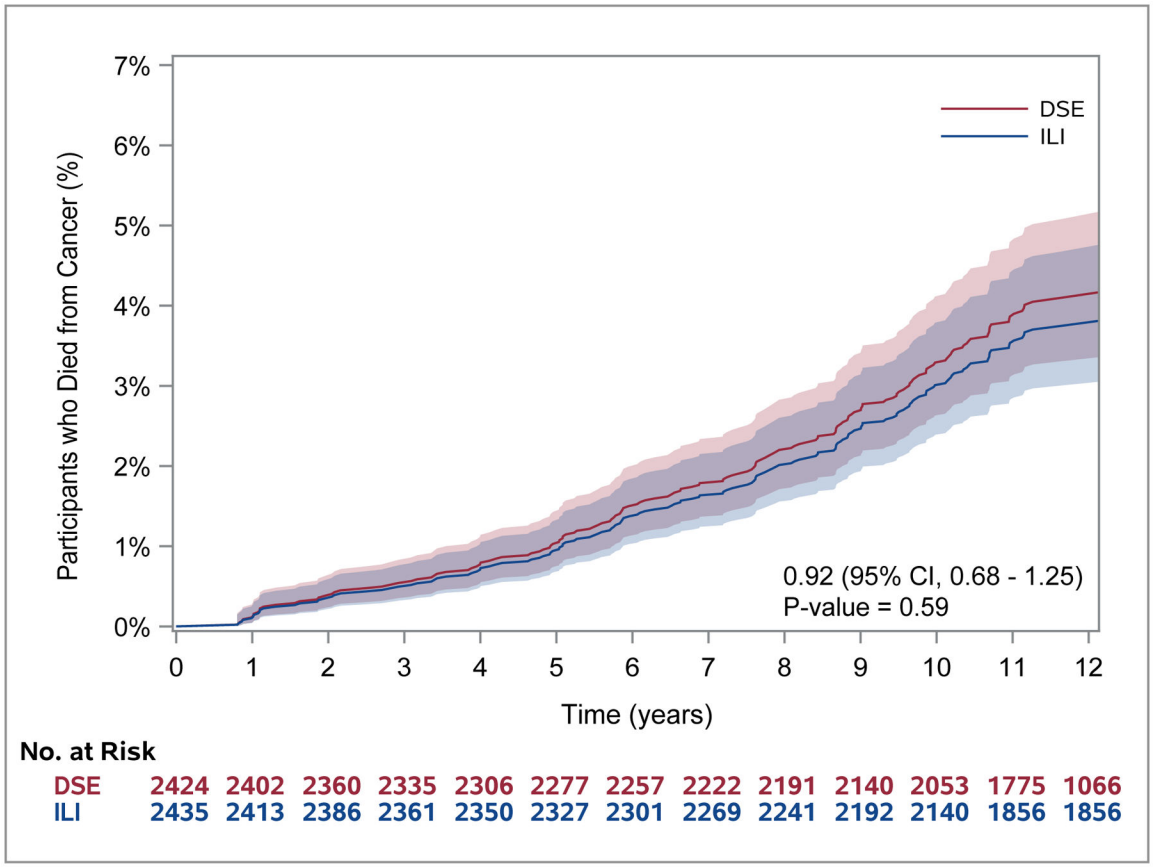

Figure 2c:
Cumulative probability of cancer mortality

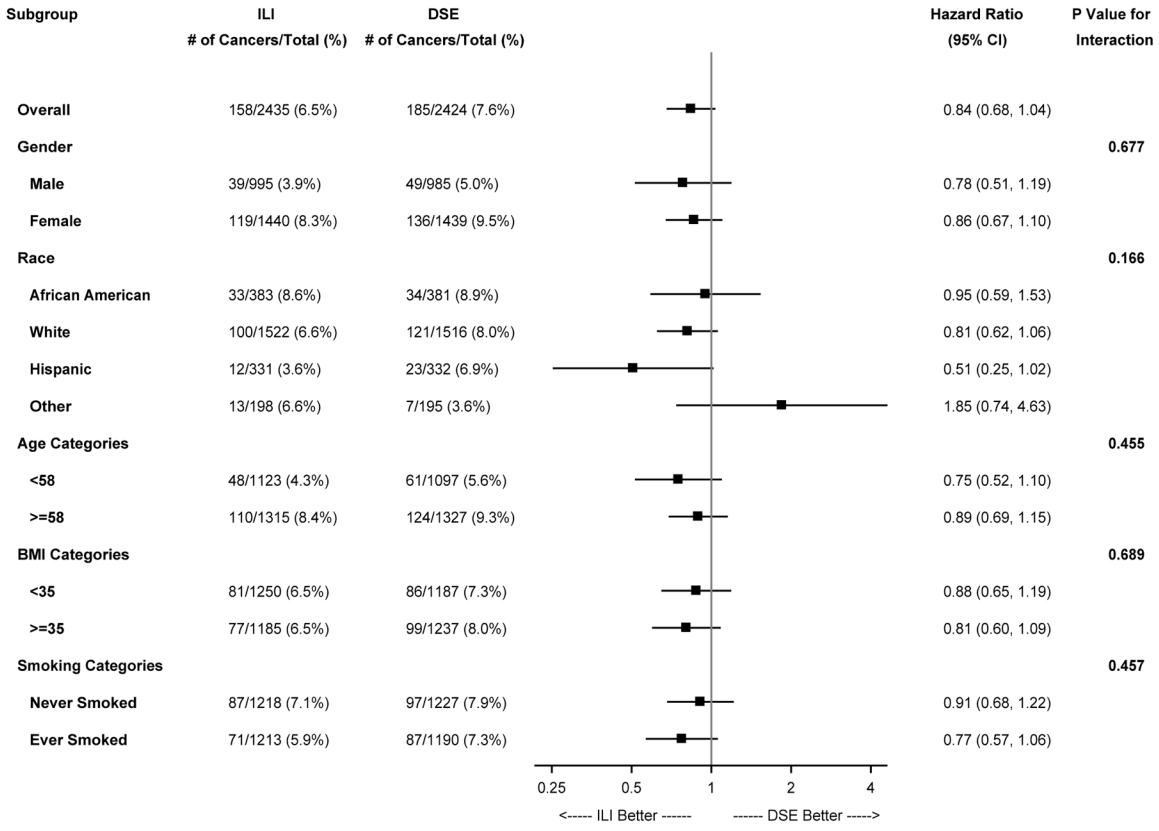

Figure 3:
Hazard ratios (95% CI) of obesity related cancer for randomization arm in subgroups

Table 1.

Baseline Characteristics of the Study Participants included in the Cancer Outcomes Analysis

Characteristics	DSE (N = 2424)	ILI (N = 2435)
Age (years)	58.7±6.82	58.42±6.76
Female	1439 (59.36)	1440 (59.14)
Race		
African American	381 (15.72)	383 (15.74)
White	1516 (62.54)	1522 (62.53)
Hispanic	332(13.7)	331 (13.6)
Other	195(8.04)	198(8.13)
Education		
<13 years	493 (20.89)	483 (20.2)
13–16 years	913 (38.69)	891 (37.26)
>16 years	954 (40.42)	1017 (42.53)
Smoking		
Never	1227(50.77)	1218(50.1)
Past	1087 (44.97)	1101 (45.29)
Current	103 (4.26)	112 (4.61)
Drinking		
None/wk	1637 (67.76)	1651 (68.05)
1–3/wk	460 (19.04)	479 (19.74)
4+/wk	319 (13.2)	296 (12.2)
Height (feet)	5.49±0.33	5.49±0.32
Weight (lbs)	222.19±41.96	221.71+43.35
BMI (kg/m^2)	36±5.77	35.93±6.02
Waist Circumference (cm)	114.08±13.69	113.86±14.35
SBP (mmHg)	129.57±17.08	128.1±17.18
DBP (mmHg)	70.46±9.55	69.9±9.54
HbA1c(%)	7.32±1.21	7.25±1.15
eGFR($mL/min/1.73m^2$) *	93.94±22.22	94.63±23.16
Cholesterol (mg/dL)	190.28±37.05	191.07±38.34
Triglycerides (mg/dL)	152 (107,217)	154 (110,220)
Insulin Use	385 (16.5)	371 (15.75)
Statin Use	1052(44.5)	1080(45.47)
History of CVD	324 (13.37)	343 (14.09)
Hypertension	2006 (82.76)	2036 (83.61)
Family History of Diabetes	1631 (67.29)	1540 (63.24)
Self-Reported Diabetes Duration (years)	5 (2,10)	5 (2,10)

DSE: Diabetes Support and Education. ILI: Intensive Lifestyle Intervention.

N (%) or mean ± standard deviation (SD) or Median (Q1,Q3). There were no significant differences (P<0.05) between the two groups, except for SBP (p<0.01), DBP (p=0.04), HbA1c (p=0.04) and family history of diabetes (p<0.01).

* eGFR calculated by Modification of Diet in Renal Disease (MDRD) Study equation

Table 2.

Cancer incidence by study arm in 4,859 Look AHEAD participants

	DSE		ILI			
Cancer Type	**Number of Events**	**Rate***	**Number of Events**	**Rate***	**HR (95% Cl)**	**P-value**
All Cancers	352	14.2	332	13.2	0.93(0.80, 1.08)	0.32
Obesity Related¶	185	7.3	158	6.1	0.84(0.68, 1.04)	0.10
Non-Obesity Related	167	6.6	174	6.7	1.02(0.83,1.27)	0.83
Men						
All Cancers	177	18.2	165	16.6	0.91 (0.74, 1.12)	0.38
Obesity Related¶	49	4.8	39	3.7	0.78(0.51,1.19)	0.25
Non-Obesity Related	128	13.0	126	12.5	0.96(0.75, 1.22)	0.73
Women						
All Cancers	175	11.6	167	11.0	0.94(0.76, 1.16)	0.58
Obesity Related¶	136	9.0	119	7.7	0.86(0.67, 1.10)	0.23
Non-Obesity Related	39	2.5	48	3.0	1.22(0.80,1.86)	0.36

DSE: Diabetes Support and Education. ILI: Intensive Lifestyle Intervention. HR: hazard ratio

*Rate per 1,000 person-years

¶Included esophagus, colon, rectum, kidney, pancreas, stomach, liver, gallbladder, thyroid, and multiple myeloma in men and women, and additional uterus, ovary, post-menopausal breast in women.

Table 3.

Cancer Mortality by study arm in 4,859 Look AHEAD participants

	DSE		ILI			
Cancer Type	**Number of Events**	**Rate***	**Number of Events**	**Rate***	**HR (95% Cl)**	**P-value**
All Cancers	85	3.2	80	3.0	0.92(0.68, 1.25)	0.59
Obesity Related¶	45	1.7	42	1.6	0.91(0.60, 1.39)	0.67
Non-Obesity Related	40	1.5	38	1.4	0.93(0.60, 1.45)	0.74
Men						
All Cancers	50	4.8	39	3.6	0.75(0.50, 1.15)	0.19
Obesity Related¶	24	2.3	17	1.6	0.69(0.37,1.28)	0.24
Non-Obesity Related	26	2.5	22	2.1	0.82(0.46, 1.44)	0.48
Women						
All Cancers	35	2.2	41	2.6	1.15(0.73, 1.81)	0.54
Obesity Related¶	21	1.3	25	1.6	1.17(0.65, 2.08)	0.60
Non-Obesity Related	14	0.9	16	1.0	1.13(0.55,2.31)	0.74

DSE: Diabetes Support and Education. ILI: Intensive Lifestyle Intervention. HR: hazard ratio

*Rate per 1,000 person-years

¶Included esophagus, colon, rectum, kidney, pancreas, stomach, liver, gallbladder, thyroid, and multiple myeloma in men and women, and additional uterus, ovary, post-menopausal breast in women.