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Randomized Study of Metformin and Intensive Lifestyle Intervention on Cancer Incidence over 21 years of follow-up in the Diabetes Prevention Program

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Abstract

Meta-analyses have reported a decrease in overall cancer incidence of approximately 10–40% with metformin use among individuals with diabetes. Lifestyle change could potentially reduce cancer incidence. The objective was to determine whether metformin or intensive lifestyle intervention (ILS) reduces the risk of cancer among adults at high risk of diabetes. The Diabetes Prevention Program (DPP, 1996–2001) randomized 3234 participants to ILS, metformin (850 mg twice daily), or blinded placebo. During follow-up through the DPP Outcomes Study (DPPOS), all participants were offered a modified lifestyle intervention, and metformin continued open-label metformin group. Participants reported cancer cases annually. Medical records were adjudicated for all reported events. The primary endpoint was total cancer incidence, comparing metformin versus placebo, with ILS versus placebo as a secondary objective. After a median follow-up of 21 years, 546 participants (173 metformin, 182 ILS, and 191 placebo) were diagnosed with a first incident cancer. Incidence rates of cancer were 9.8, 10.5, and 10.8 per 1,000 person-years

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in metformin, ILS, and placebo, respectively, with a hazard ratio (HR) of 0.90 (95%CI = 0.73 to 1.10) for metformin compared to placebo and 0.96 (95%CI = 0.79 to 1.18) for ILS compared to placebo. There were no differences between any treatment groups for obesity-related cancer or in sex-specific analyses. Neither assignment to metformin nor ILS reduced cancer incidence among adults at high risk of diabetes. These results may be impacted by increased non-study metformin usage over time due to the development of diabetes and reduced intensity of ILS intervention over time.

INTRODUCTION

Type 2 diabetes (T2D) and obesity are closely linked and increasingly recognized as important risk factors for the development of cancer¹. Excess body weight has been estimated to account for 25–50% of cases of some common cancers (breast, colorectal, endometrial, renal cell, esophageal), with 13 cancer types now considered obesity-related². Metformin, widely used as first line treatment for T2D, has received attention as a potential anti-cancer agent, based on promising experimental and epidemiologic data^{3,4}. A meta-analysis of 11 observational studies showed a 31% reduction in cancer incidence in patients taking metformin compared with other glucose-lowering drugs, and a 34% reduction in cancer mortality⁵. Potential mechanisms for metformin's anti-cancer actions include direct insulin-independent anti-tumor effect via activation of the cellular energy signal AMPK⁶, and indirect effects via reduction in hyperinsulinemia. Benefits of metformin against breast, colorectal, pancreas, endometrial and prostate cancer have been suggested, but phase III clinical trials to date have had insufficient follow-up for cancer outcomes and early phase trials have focused largely on biomarkers and surrogate outcomes⁷. A phase III randomized trial of metformin for breast cancer in the adjuvant setting with 5 years of follow-up found no improvement in breast cancer outcomes⁸.

Lifestyle change, in particular, dietary weight loss interventions, for obesity or T2D treatment or prevention could potentially reduce cancer incidence. Recent data published from Look AHEAD, a randomized trial of intensive lifestyle intervention (ILI) versus diabetes support and education (DSE) in 4,859 participants with T2D, showed a 16% (95% confidence interval 0.68 to 1.04) lower incidence of obesity-related cancers after a median of 11 years of follow-up, 332 in ILI and 352 in DSE. There were no differences in total cancer incidence or cancer mortality⁹. Surgically-induced weight loss may have beneficial effects on cancer. Long-term follow-up of patients with diabetes in the Swedish Obese Subjects (SOS) study reported reduced cancer incidence in patients who had undergone bariatric surgery compared to conventional obesity treatment (HR 0.63, 95%CI 0.44–0.89) and durable diabetes remission in these patients was associated with reduced cancer risk¹⁰.

The Diabetes Prevention Program (DPP), initiated in 1996, randomized adults at high risk for T2D, defined by evidence of impaired glucose regulation and the presence of overweight or obesity, to either an intensive lifestyle intervention (ILS) with a goal of 7% body weight loss, metformin 850 mg twice a day or blinded placebo. Follow-up in the blinded phase of the study continued for an average of 3.2 years. Long term follow-up of the cohort, continued in the DPP Outcome Study (DPPOS) until 2020¹¹ and included open-label

metformin treatment and periodic group lifestyle sessions. We reported that cancer was the leading cause of death in the cohort¹², consistent with malignant neoplasms being the leading cause of death in U.S. adults aged 45–64 years¹³. The present report examines the effect of metformin and ILS on cancer risk in DPP/DPPOS participants with the hypothesis that metformin and/or weight loss would reduce the risk of cancer in this cohort of adults at high risk for cancer because of prediabetes/T2D and obesity.

MATERIALS AND METHODS

Trial Design

From 1996 to 1999, DPP enrolled 3234 adults at high risk of developing diabetes as described elsewhere¹¹. Key inclusion criteria were adults age 25+, impaired glucose regulation (fasting plasma glucose 100–125 mg/dl and 2-hour 75g OGTT glucose 140–199 mg/dl) and the presence of overweight or obesity (BMI ≥ 25 kg/m²). Participants were randomly assigned to one of three interventions: intensive lifestyle (ILS) aimed to achieve and maintain a 7% weight loss and 150 min or more per week of moderate-intensity physical activity, or double-blind metformin 850 mg twice per day, or matching placebo. The lifestyle intervention has been previously described in detail¹⁴ and is available online through the Centers for Disease Control. The DPP study was ended in 2001 one year ahead of schedule when it was established that ILS reduced the incidence of diabetes by 58% and metformin reduced the incidence by 31% compared to placebo¹⁵. Study interventions were safe, as previously reported^{15,16}. During a one-year bridge period, participants were informed of the main study results, those assigned to metformin or placebo were unblinded, and all participants were offered a group-administered version of the lifestyle curriculum prior to initiation of DPPOS in 2002¹⁷. DPPOS enrolled 2779 (88%) of the original surviving participants, including 767 participants who had been diagnosed with diabetes. Group lifestyle sessions were offered to all participants every 3 months until 2014, and booster lifestyle sessions were offered to participants in the original ILS group twice annually through 2014. Those previously assigned to the metformin group continued to receive metformin 850 mg twice daily open label, unless the drug was discontinued for safety reasons or participants had developed diabetes with a fasting glucose of 140 mg/dl or more in DPP or glycated hemoglobin (HbA1c) of 7% or more in DPPOS, at which time, according to the protocol, medication management deferred to their own primary care provider.¹⁸ In 2012, incident cancer was added as a study outcome. Written informed consent was obtained from all participants, consistent with the Declaration of Helsinki and the study amendments were approved by each clinical center's responsible institutional review board. Participants provided written informed consent after discussion with study staff. Physical activity was recorded for all participants using the MAQ to estimate the leisure physical activity as met hours per week¹⁹. Trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00004992) Identifier: [NCT00004992](https://clinicaltrials.gov/ct2/show/study/NCT00004992), [NCT00038727](https://clinicaltrials.gov/ct2/show/study/NCT00038727).

Ascertainment of Cancer Outcomes

Following randomization in DPP, incident cancer cases were ascertained at each annual follow-up visit and/or were reported as a serious adverse event if there was hospitalization or death. In 2012, retrospective collection of medical records associated with the reported

events was undertaken. Medical records were collected prospectively from 2012 onward. Detailed clinical records, including pathology reports, were sought from treating physicians or healthcare institutions. A National Cancer Institute (NCI) staff oncologist, blinded to participant treatment group and metformin use, conducted adjudication according to the Surveillance, Epidemiology, and End Results (SEER) Program guidelines 2012²⁰. In addition, cancer cases reported through death certificate were included. Reports of cancer were categorized as not cancer/not reportable, primary incident case, primary non-incident case, recurrence of a non-incident case, or recurrence of an incident case. Primary incident cases (primary events that occurred after randomization) were included in this analysis. If a participant experienced cancer at additional anatomical sites, only their first occurrence contributed to the composite cancer analyses, while their first occurrence of each specific anatomical-type contributed to the individual anatomical-type analysis. A questionnaire about cancer risk factors and cancer screening habits was conducted in 2012 and screening history was subsequently collected annually. Obesity-related cancer was defined as meningioma, multiple myeloma, or cancer of the esophagus, kidneys, uterus, ovaries, thyroid, breast (postmenopausal), liver, gallbladder, upper stomach, pancreas, colon, and rectum. The remainder of cancer types were considered as nonobesity-related². Only cancer sites where the total number of cases across the groups was greater than 20 were analyzed individually.

Statistical Analysis

Primary analyses used the “intention-to-treat” paradigm including all participants and data as of the data lock on February 23, 2020. Cumulative incidence rates accounted for competing risk due to non-cancer deaths using Fine-Gray’s estimates²¹ in Cox proportional hazards models to assess treatment and covariate effects that may mediate or moderate treatment effects. Censoring date for the analysis was the date of last participant contact or the date of death, whichever was later. Follow-up after the last visit was included only in the event of participant death, which provides a better estimate of cancer incidence among participants who are deceased but overestimates incidence overall if mortality is associated with cancer²². The primary analysis used the first incident cancer event based on adjudication. It was determined a priori that this analysis would be performed when 170 events had occurred in the placebo group, such that the primary comparison of metformin vs. placebo had 85% power for a 2-sided significance level of 0.05, to detect a 28% risk reduction in total cancer based on prior observational data using a log-rank test³. ILS compared to placebo was a secondary outcome, as were treatment comparisons of site-specific cancer incidence such that individuals could have contributed to multiple cancer sites.

Interaction of each subgroup x treatment assessed the heterogeneity in treatment effects in prespecified baseline subgroups (sex, age, race/ethnicity, and baseline BMI) as well as post-randomization defined time-dependent subgroup for diabetes status without adjustment for multiplicity.

Sensitivity analyses were conducted to address factors that may have affected treatment response: 1) exclusion of participants with a personal history of cancer prior to

randomization, 2) exclusion of cancers diagnosed within a year of randomization and 3) exclusion of cases adjudicated based solely on a death certificate. Extended follow-up increased the likelihood that time-varying confounders due to intercurrent event of diabetes may have attenuated the hypothesized effect of randomized metformin compared to placebo. Additional Cox models assessed the effect of lifestyle and metformin compared to placebo after adjustment for cancer risk factors and out-of-study metformin use to explore these potential sources of confounding²³. The etiologic effect of metformin was explored using marginal structural models (MSM) with truncated inverse probability censoring weighting (IPCW) and instrumental variable (IV) approach to account for out-of-study metformin and discontinuation of randomized metformin^{24–26}. Each method makes different assumptions about the observed data and their relationships and may reach different conclusions about the metformin effects to evaluate the complex and heterogeneous metformin effects.

Notation. We start by defining notation.

- $X_1(t)$, $X_2(t)$: actual metformin exposure at time point t – the indicator of taking metformin ($X_1(t)$) and the cumulative duration of taking metformin ($X_2(t)$);
- I : Randomization to the metformin group at DPP baseline;
- $Y(t)$: Cancer outcome at time t ;
- $V(t)$, $U(t)$: Observed ($V(t)$) and unobserved ($U(t)$) effect moderators that are affected by ($X_1(t)$, $X_2(t)$) and impact $Y(t)$, e.g. HbA1c level after taking metformin;
- $Z(t)$: Adjustment covariates that impact $Y(t)$, such as race/ethnicity;
- $C(t)$: Confounders that are associated with ($X_1(t)$, $X_2(t)$) and impact $Y(t)$, such as HbA1c or diabetes diagnosis during follow-up that leads to change in metformin exposure.
- *Counterfactual*: In causal inference literature, researchers speculate how the outcome would change for an individual if he had taken an alternative treatment different from what he actual received, that is, counter to the facts. A hypothetical situation that did not occur in fact but is hypothesized to occur under hypothetical conditions such as perfect follow-up or adherence to assigned interventions.

The IPCW method along with MSM attempts to correct the imbalance between actual metformin takers versus non-takers in 2 steps²⁴. The first step of the IPCW method censors participants when they switch treatments, i.e., participants who were randomized to the metformin group who stopped taking study metformin or placebo participants who started taking out-of-study metformin. This treatment censoring may be informative (i.e., not occurring at random) due to factors that are also associated with the outcomes. The second step of the IPCW method is to correct this informative censoring using weighted analyses. The weights are calculated as the inverse probability of having remained on the randomized assignment given a set of specified factors which are assumed to be related to both the probability of switching treatment and the outcome. The weights create a pseudo- or counterfactual population as if the participants had complied with their treatment

assignments. The last step is to use a Cox MSM to estimate the treatment effect in the weighted population where participants who are censored due to switching off their assigned treatment are represented by other uncensored participants who are similar in terms of the specified confounders. Assuming all measured confounders are specified and there are no unmeasured confounders, and correct model specifications, the obtained estimator represents the counterfactual effect of the treatment on the outcome in a hypothetical setting where all participants remained on their randomized treatment. This method, however, does not account for informative loss to follow-up, i.e., not switching treatments but withdrawing or becoming lost. The MSM approach used the Stage 1 model to derive the weights using switch defined as either start of metformin in the Placebo group or stopping metformin in the metformin group with adjustment for age, race/ethnicity, sex, LDL meds, lipid, smoking, fasting glucose, 2 hour glucose, Hba1c, fasting insulin, alcohol use, family history of diabetes, hypertension, BMI, urine albumin-creatinine ratio and eGFR by ckd-epi. Stage 2 MSM included time dependent HbA1c and The IV method uses two-stage-residual-inclusion to derive the counterfactual effects of taking metformin, considering the presence of unmeasured confounding caused by treatment crossover²⁵. The first stage is a generalized linear model using metformin randomization, I , as the instrumental variable to predict the observed metformin usage $X(t)$, adjusting for characteristics $Z(t)$. Residuals in such models are independent from the metformin randomization and can be viewed as a summary of the confounders leading to extra or less metformin taking, $C(t)$. In the second stage, the Cox models for the time to incident cancer, outcome $Y(t)$, are fitted adjusting for both $X(t)$ and residuals from the first stage. By adjusting for the residuals, we adjust for unmeasured confounders leading to individual-level less or extra metformin taking compared to their original assignments. Therefore, the effects of the observed metformin indicator in the second stage can be interpreted as the causal effects of metformin taking, i.e., the difference in the outcomes between participants taking or not taking metformin when potential confounders are adjusted through the residuals. Models in Stages 1 and 2 of the IV approach adjusted for age, race/ethnicity, sex, family history of diabetes, smoking, alcohol use, and BMI. All p-values are two-sided, with nominal statistical significance level of 0.05. All statistical analyses were performed with SAS 9.4 and R 3.5.2.

Data Availability

DPP/DPPOS has provided the protocols and lifestyle and medication intervention manuals to the public through its public website (<https://dppos.bsc.gwu.edu/web/dppos>). The DPPOS abides by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) data sharing policy and implementation guidance as required by the NIH/NIDDK (<https://repository.niddk.nih.gov/studies/dppos/>).

RESULTS

Participants

The CONSORT flow of the randomized cohort is shown in Figure 1. Baseline characteristics of the participants are presented in Table 1. Treatment groups were well balanced in terms of established cancer risk factors including smoking, alcohol use, BMI, and family history

of cancer. At baseline, 141 (4.4%) participants reported a diagnosis of cancer prior to randomization. During DPP, adherence to metformin, defined as taking at least 80% of study prescribed pills, was about 70% and fell to ~50% during DPPOS¹⁸ (Figure 2). Metformin exposure across all study arms increased over time as some participants developed diabetes and were treated by their primary care provider outside of the study protocol. The mean metformin exposure time in the metformin arm after 21 years of median follow-up was 11.3 years (9.9 years of which were study metformin) compared to 2.7 years in the placebo group and 2.1 years in the ILS group (Figure 2). Participants in the ILS group achieved the weight loss and physical activity goals during the first study year, although there was subsequent weight re-gain and treatment group differences were attenuated over time (Figure 2). Of note, weight declined in all treatment groups during the later years of follow-up (~10–20), consistent with an aging cohort. Cancer screening in this cohort was very high when first collected in 2012, with over 96% of participants reporting screening for cancer at least once, mammogram and pap smears reported in 97% and 86% of women respectively, PSA tests reported by nearly three-quarters of men, and colorectal screening reported by 85% of the cohort (Table 1). There was no significant difference in cancer screening across randomized treatment groups.

Cancer Incidence

During the retrospective collection of medical records, more than 98% of cases were adjudicated and approximately 96% of adjudicated events were classified as cancer. During the prospective collection of medical records, approximately 93% of cases were adjudicated and 96% of adjudicated events were classified as cancer. A death certificate was available as the only source of information in 7% of adjudications. During a median follow-up of 21 years, 173 participants in the metformin group had a first incident cancer compared to 191 participants in the placebo group and 182 participants in the ILS group (Table 2). The cumulative incidence (Figure 3) was 20.3% in the metformin group compared with 22.3% in the placebo group and 21.6% in the ILS group. Of all cancer events, approximately one half were categorized as obesity-related.

Randomization to metformin was not associated with incidence of total cancer risk (HR=0.90, 95% CI=0.73 to 1.10, p=0.31), obesity-related cancer risk (HR= 0.89, 95% CI=0.66 to 1.18, p=0.41), or non-obesity-related cancer risk (HR=0.93, 95% CI 0.69 to 1.24, p=0.61) compared to placebo (Table 2). Supplemental Table S1 examines the effect of randomization to metformin and ILS compared to placebo on the incidence of individual anatomical cancer sites. Randomization to metformin compared to placebo was not associated with a reduced risk in any of the individual cancer sites except kidney (HR=0.27, 95% CI=0.09 to 0.80, p=0.02) (Supplemental Table S1).

Randomization to ILS was not associated with a decrease in total cancer risk (HR=0.96, 95% CI=0.79 to 1.18, p=0.72), obesity-related cancer risk (HR= 0.93, 95% CI=0.70 to 1.23, p=0.61), or non-obesity-related cancer risk (HR=1.0, 95% CI=0.75 to 1.34, p=0.97) compared to placebo. ILS was not associated with a reduced risk of cancer in any of the individual cancer sites analyzed compared to placebo.

The effect of metformin and ILS stratified by age group, sex, race, BMI group, and time dependent diabetes status are shown in Figure 4. The effect is similar across the prespecified subgroups with no interaction between treatment effect and subgroup (Supplemental Table S2). The time varying effects of the interventions were also examined through a test of proportional hazards assumption of the ILS or metformin effects and through an interaction of treatment by the time periods defined by DPP (3.2 average years) or post-DPP. In both sets of analyses, the effect of ILS or metformin did change over time.

To further evaluate potential confounding due to demographics and cancer risk factors, adjusted models (Supplemental Table S3) showed that the risk of cancer in the metformin or ILS groups compared to placebo remained unchanged (metformin vs. placebo HR=0.86, 95% CI=0.69 to 1.06, p=0.16; ILS vs placebo HR=0.93, 95% CI=0.76 to 1.14, p=0.47). In sensitivity analyses, adjustments for personal cancer history, cases occurring within a year of randomization, and method of adjudication did not appreciably change the results. Due to the increasing out-of-study metformin use in all three randomized groups over time, models were constructed to explore the potential mediating effects of diabetes status and duration, and cumulative glycemic and metformin exposure (Supplemental Table S4). These models also did not change the overall result of the study. The lowest estimated hazard ratio based on a marginal structural model accounting for time dependent HbA1c for the effect of metformin vs. placebo was HR=0.81, 95% CI=0.61 to 1.09, p=0.16). The instrumental variable approach resulted in HR=0.83, 95% CI=0.63 to 1.08) for total cancer.

Discussion

Given the association of diabetes with increased cancer risk, DPP/DPPOS interventions, which had a durable effect on lowering diabetes incidence¹⁸, might be expected to lower cancer incidence as well. Further, available evidence suggests that both weight loss and metformin could have beneficial effects on cancer risk, independent of their efficacy to prevent diabetes. We previously reported that cancer was the leading cause for mortality in the DPP/DPPOS cohort, with no differences between treatment arms assigned to ILS, metformin or placebo¹². Here, we compared the cancer incidence after a median follow-up of 21 years and found no difference with randomization to metformin (with a median usage of 11.3 years) or ILS compared with placebo on the incidence of either total or obesity-related cancers.

There is evidence to support a cancer protective role of metformin, with proposed mechanisms including a direct insulin-independent anti-tumor effect via activation of the cellular energy signal AMPK⁶ and inhibition of mitochondrial oxidative phosphorylation²⁷. In addition, since insulin has mitogenic effects and tumor cells often express high levels of insulin receptor, metformin's insulin lowering effects may also help reduce tumor development and growth. Following initial enthusiasm from promising observational data, there were suggestions that some of these studies had methodologic flaws including survival time bias which may have over-estimated metformin effect²⁸. More recent observational studies, including from large clinical practice databases in Israel and the UK, have failed to demonstrate lower cancer risk with metformin among patients with diabetes^{29,30}. Several randomized trials of metformin, compared to other diabetes medications, also failed to

demonstrate lower cancer incidence, although the studies were relatively small with limited duration of follow-up and relatively young median age at baseline³¹. Time-related bias, including immortal time bias and time-lag bias were proposed as early as 2012 as reasons for discrepancies in the epidemiologic evidence, notably since metformin is a first-line treatment for diabetes whereas many of the comparison groups are second and third-line therapies used later in the stage of the disease²⁸. Most recently, a large Phase III adjuvant trial comparing metformin versus placebo on invasive disease-free survival of breast cancer was published showing no impact of metformin (HR=1.01; 95% CI 0.84–1.21; P=.93)⁸. Following the results of this trial, potential pitfalls of epidemiologic studies were again noted, including potential confounding by obesity and associated hyperinsulinemia³². In DPP/DPPOS, adjusting for BMI measured longitudinally did not impact the results, although the study population had obesity or overweight at baseline and remained so throughout the course of the study. We also looked specifically at obesity-related cancers, and this did not change the overall findings of the study. Nonetheless, interest in the anti-cancer potential of metformin remains and there are numerous ongoing trials examining the potential impact of metformin both as a cancer prevention agent and as adjuvant cancer treatment. Our study provides important and perhaps more definitive data from over 20 years of randomized metformin and is unique in studying individuals at high-risk of T2D. However, there are a number of ongoing trials examining populations a high risk of cancer at specific anatomical sites which our study would not have had the power to detect. This includes a study of the impact of metformin on oral premalignant lesions ([NCT05536037](#)) as well as a study of people at risk for lung cancer ([NCT04931017](#)). These studies are both related to smoking and this risk factor was limited in the DPP/DPPOS cohort, with 7% current smoking at baseline. There is also interest in examining the effect of metformin on cancer risk in patients with Li-Fraumeni syndrome based on preliminary pilot work showing that metformin can suppress mitochondrial function in individuals with germline *TP53* pathogenic variants³³. Real world data could also be used to answer these types of questions but rigorous approaches that emulate trials must be used as outlined by Yu and Suissa³².

Although obesity is associated with cancer risk, there is limited evidence that cancer risk can be reduced through lifestyle intervention and intentional weight loss. The Women's Health Initiative (WHI) observational cohort found that among postmenopausal women who had sustained intentional weight loss (5% of body weight) for 3 years, there was a lower obesity-related cancer risk (HR = 0.88, 95% CI 0.80 to 0.98)³⁴. When stratified by BMI, this lower risk was limited to women with baseline obesity³⁴. Bariatric surgery can result in more substantial weight loss of up to 20–25% of body weight and is often maintained for a decade or more. A recent study from Cleveland Clinic showed that weight loss achieved with bariatric surgery was associated with a 32% lower risk of developing cancer ([95% CI, 0.53–0.87], P = .002) and a 48% lower risk of cancer-related death ([95% CI, 0.31–0.88], P = .01) compared with adults who did not have the surgery³⁵. This is similar to the effect size reported in the SOS¹⁰. In DPP/DPPOS, examination of cancer risk 21 years after randomization showed no modification of the risk of obesity-related or non-obesity-related cancer when comparing ILS to placebo. Following initial weight loss in the ILS group of close to the target 7% of body weight (6.8 kg loss at year 1), there was gradual weight

re-gain over time, although weight remained modestly lower in the ILS group compared to placebo during DPPOS³⁶. Self-reported physical activity was initially higher in the ILS group, but these differences also attenuated over time. Look AHEAD, a randomized clinical trial of a weight loss intervention (ILI) in adults with type 2 diabetes, achieved a mean ($\pm$ SE) weight loss of $8.5\pm 0.2\%$, compared to $0.6\pm 0.2\%$ in the control group at year 1. However, these differences were not sustained over time and, the reported hazard ratio for obesity-related cancer was 0.84 (95% CI: 0.68–1.04). Significant and sustained weight loss may be key to reducing the risk of obesity-related cancer. There is a large ongoing trial of lifestyle intervention based on the DPP and Look AHEAD interventions in women previously diagnosed with breast cancer³⁷. Accrual was completed in February 2021 and participants will be followed for up to 10-years for survival related outcomes. In breast cancer, the WHI dietary modification trial showed that women who were randomized to a 20% reduction in fat intake which resulted in modest weight loss showed no reduction in breast cancer incidence or overall survival but deaths after breast cancer were significantly lower by 15% (0.74 to 0.96; $P = .01$) after a median followup of 19.6 years³⁸.

The strengths of the current analyses include the longest randomized trial of metformin and carefully documented total metformin exposure, near-complete ascertainment of incident cancer cases over a follow-up period of up to 21 years, expert cancer adjudication based on medical records, and detailed information about cancer risk factors, including smoking, alcohol use and family history as well as cancer screening information. Further, many important covariates (e.g., out of study metformin use, weight changes over time, incident diabetes, blood glucose, HbA1c) were available for inclusion in time-dependent multivariate models. This study is generalizable to adults with characteristics similar to those of DPP participants at high risk for type 2 diabetes, which represents over 30% of the adult US population³⁹.

Limitations

A significant limitation to this intention to treat analysis is the increasing use of metformin in the ILS and placebo groups over time. However, adjusted analyses and marginal structural models including this “cross-over treatment” did not appreciably change our results. Cross-over has the potential to impact any trial but a study where the prevention intervention under investigation is also the first line intervention for the disease being prevented faces increasing risk to the randomized analyses over time. In addition, adherence to study metformin declined over time, although there remained a wide difference in total metformin exposure between the groups. The intensity of the ILS intervention was not sustained after the initial 3.2 years and limited lifestyle intervention was offered to all treatment groups during DPPOS, leading to reduced differences in weight between the groups. Finally, the study was powered to detect a 28% reduction in cancer cases (metformin vs. placebo) and was underpowered to detect smaller differences as well as underpowered to examine individual anatomical sites or subgroups.

Conclusions

DPPOS represent the longest metformin treated cohort of individuals at risk for diabetes and a cohort in which there was significant and modestly sustained weight loss with the ILS

intervention. However, in these participants, assignment to metformin or ILS did not reduce the risk of total cancer or obesity-related cancers. Metformin use in both the placebo group and the ILS group increased over time due to the development of diabetes and the intensity of the ILS intervention was not sustained. These features may have diluted the effect of the interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Prevention Relevance Statement:

This study examines both metformin and intensive lifestyle intervention as primary cancer prevention interventions in people at high risk for type 2 diabetes.

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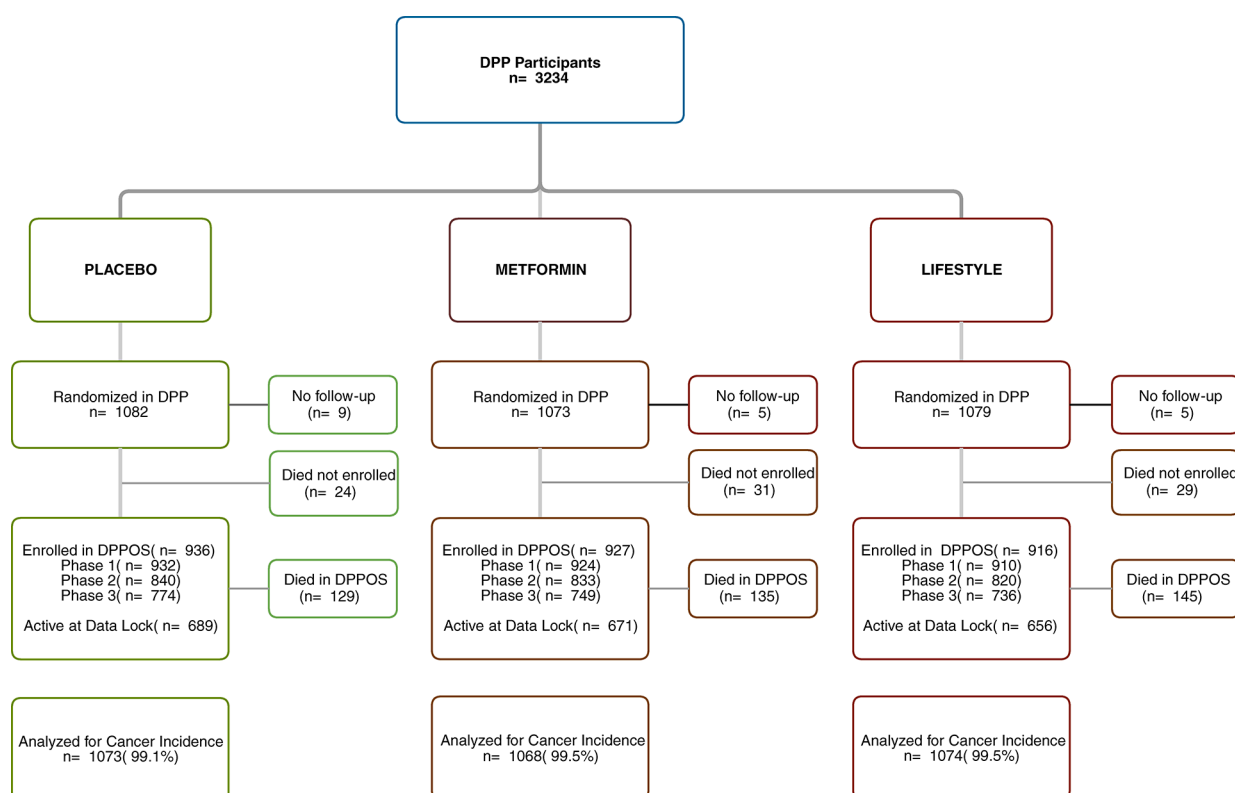


Figure 1.

Consort Flow Chart for the Diabetes Prevention Program Outcomes Study

The consort flow depicts the course of participants since original randomization in DPP to Placebo, Metformin or Lifestyle, enrollment in the Diabetes Prevention Program Outcomes Study, analytic cohort and participant status through various phases of DPPOS.

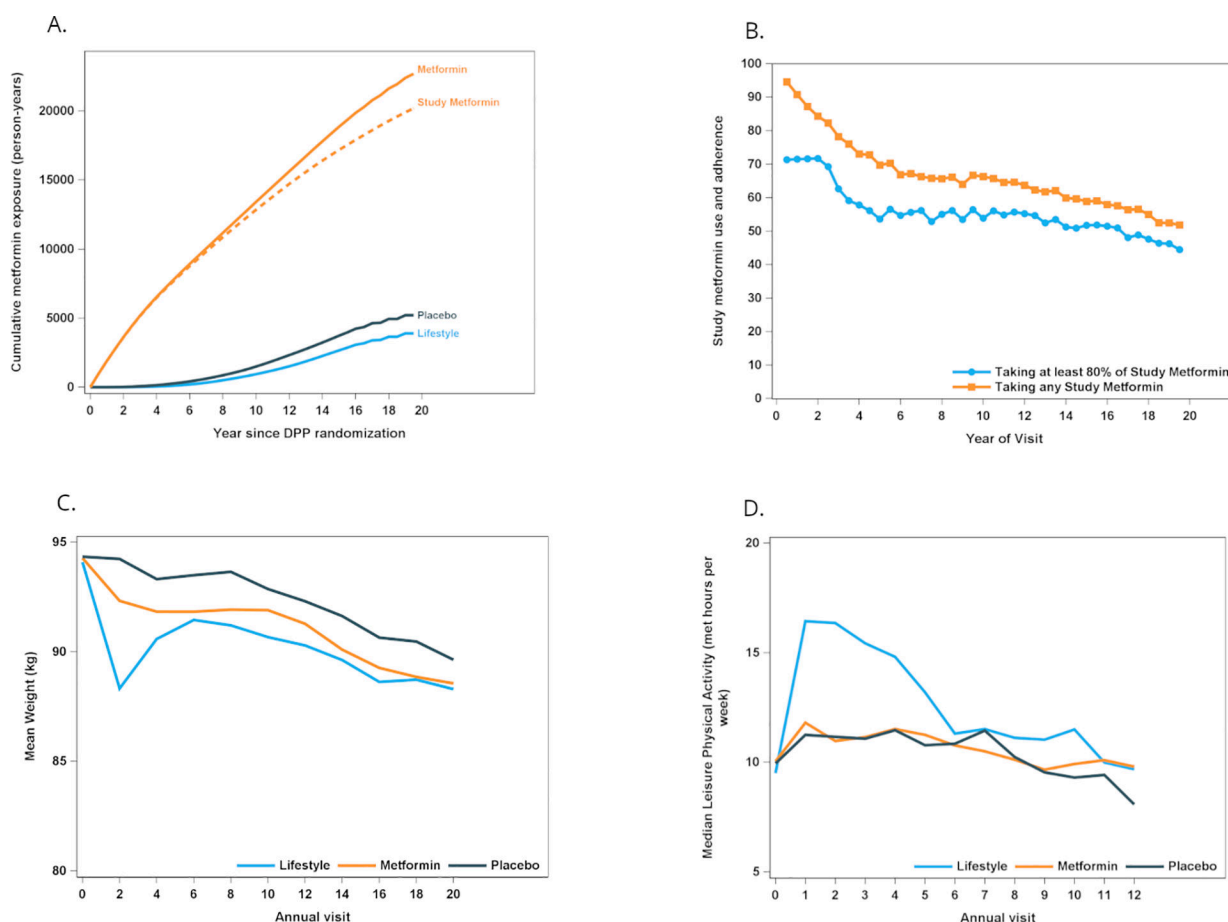


Figure 2.

Total and Study Metformin use, Weight and Physical Activity Changes by Original Randomized Group During Follow-up

(A) Cumulative metformin which includes both study and out of study use. (B) Proportion of participants taking any study metformin and use at least 80% of study metformin in participants randomized to metformin and eligible to have study metformin. By protocol, participants are no longer eligible to take study metformin when fasting glucose exceeds 140 mg/dl or more in DPP or HbA1c exceeds 7% or more in DPPOS. Participants who are no longer eligible were taken off study metformin and management referred to their primary care provider. (C) Mean weight (kg) during follow-up. (D) Median leisure physical activity is based on the MAQ.

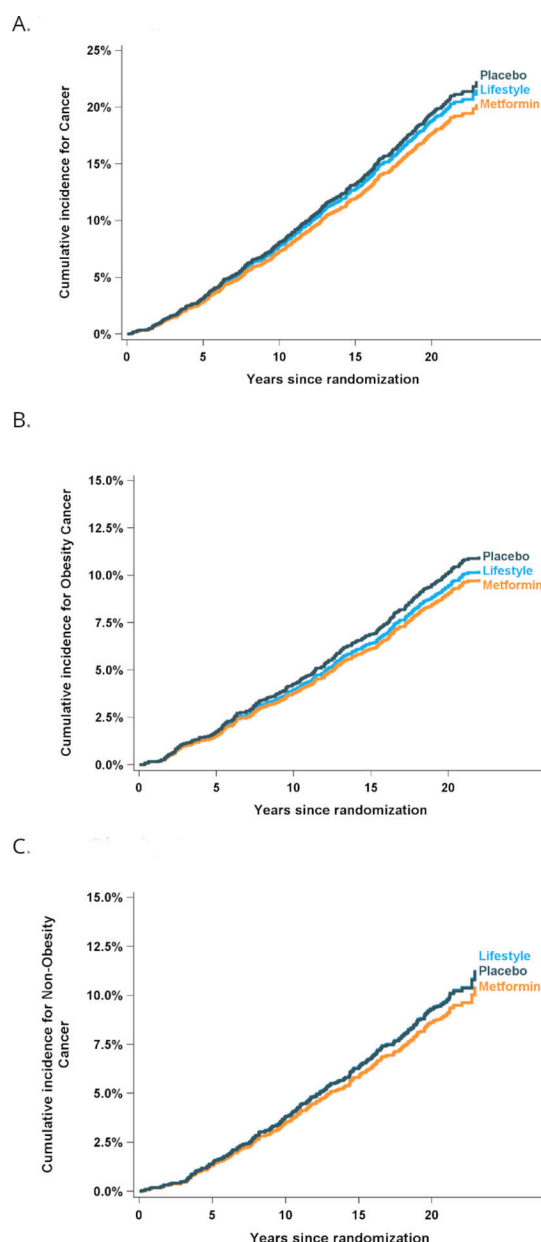


Figure 3. Cumulative Incidence for Total (A), Obesity (B), and Non-obesity (C) Cancer by Original Treatment Group

First incident cancer was used in each of the three panels. Obesity-related cancer was defined as meningioma, multiple myeloma, or cancer of the esophagus, kidneys, uterus, ovaries, thyroid, breast (postmenopausal), liver, gallbladder, upper stomach, pancreas, colon, and rectum. The remainder of cancer types were considered as nonobesity-related.

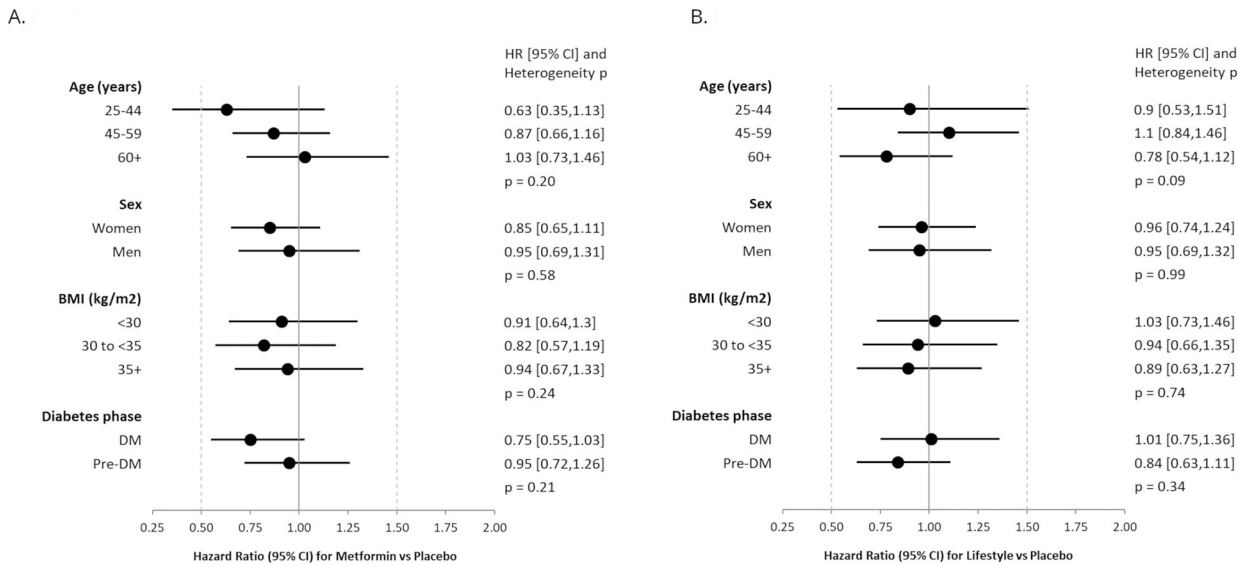


Figure 4.
Effect of Metformin versus Placebo (A) and Lifestyle versus Placebo (B) on Total Cancer Incidence by Subgroups
Treatment effects by pre-defined subgroups are expressed as hazard ratio (95% confidence interval) with heterogeneity p-value assessed using interaction of subgroup x original randomized groups. All subgroups were assessed at baseline except for diabetes status which was a time varying subgroup.

Table 1:
Baseline characteristics of participants by DPP randomization.

Characteristic	Total (n=3234)	Placebo (n=1082)	Metformin (n=1073)	Lifestyle(n=1079)	p-value
Age (years)	50.6 ± 10.7	50.3 ± 10.4	50.9 ± 10.3	50.6 ± 11.3	0.45
Women (%)	2191 (68%)	747 (69%)	710 (66%)	734 (68%)	0.35
Race/Ethnicity					0.49
White	1768 (55%)	586 (54%)	602 (56%)	580 (54%)	
African-American	645 (20%)	220 (20%)	221 (21%)	204 (19%)	
Hispanic	508 (16%)	168 (16%)	162 (15%)	178 (16%)	
American Indian	171 (5%)	59 (6%)	52 (5%)	60 (6%)	
Asian	142 (4%)	49 (5%)	36 (3%)	57 (5%)	
Education (%)					0.80
Primary	130 (4%)	51 (5%)	36 (3%)	43 (4%)	
High school	704 (22%)	234 (22%)	233 (22%)	237 (22%)	
College	1556 (48%)	520 (48%)	514 (48%)	522 (48%)	
Graduate school	844 (26%)	277 (26%)	290 (27%)	277 (26%)	
Smoking					0.74
Never	1897 (58.7%)	635 (58.7%)	634 (59.1%)	628 (58.2%)	
Current	226 (7.0%)	84 (7.8%)	72 (6.7%)	70 (6.5%)	
Former	1111 (34.4%)	363 (33.5%)	367 (34.2%)	381 (35.3%)	
BMI (kg/m ²)	34.0 ± 6.7	34.2 ± 6.7	33.9 ± 6.6	33.9 ± 6.8	0.59
Waist (cm)	105 ± 14	105 ± 14	105 ± 14	105 ± 15	0.85
Fasting glucose (mg/dL)	106 ± 8	107 ± 8	107 ± 8	106 ± 8	0.45
HbA1c (%)	5.91 ± 0.50	5.91 ± 0.51	5.91 ± 0.50	5.91 ± 0.50	0.99
Fasting insulin	24 [16, 33]	24 [16, 33]	24 [16, 34]	23 [16, 33]	0.62
Weekly alcohol use					0.70
<1 drink	74%	75%	74%	76%	
1–7 drinks	20%	21%	21%	19%	
>7 drinks	5%	4%	5%	5%	
Personal history of cancer	4.4%	3.4%	4.6%	5.1%	
Family history of cancer [†]					0.36
Yes	41%	40%	42%	40%	
No	29%	31%	29%	28%	
Unknown	30%	29%	30%	32%	
Ever screened [†]					
Breast in women	1513/1558 (97%)	516/534 (97%)	503/516 (97%)	494/508 (97%)	0.70
Prostate	515/710 (73%)	164/233 (70%)	187/245 (76%)	164/232 (71%)	0.26
Cervical	1349/1558 (86%)	466/534 (87%)	439/516 (85%)	444/508 (87%)	0.47
Colorectal	1927/2268 (85%)	645/767 (84%)	650/761 (85%)	632/740 (85%)	0.71

Data are means (SD) or %.

* p<0.05 Metformin vs Placebo or Lifestyle vs Placebo. #p<0.05 Metformin vs. Lifestyle

[†]Collected in 2012

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Table 2.

First Incident Cancer (Obesity and nonobesity-related) by Treatment Group

	Number of Events			Event Rate/1000 person-years			Hazard Ratio (95% CI); p-value	
	Placebo (PLB)	Metformin (MET)	Lifestyle (ILS)	Placebo	Metformin	Lifestyle	MET vs PLB	ILS vs PLB
Total Cancer	191	173	182	10.8	9.8	10.5	0.90 (0.73, 1.10) p = 0.31	0.96 (0.79, 1.18) p = 0.72
Obesity-related	99	88	91	5.4	4.8	5.1	0.89 (0.66, 1.18) p = 0.41	0.93 (0.70, 1.23) p = 0.61
Nonobesity-related	92	85	91	5.0	4.6	5.1	0.93 (0.69, 1.24) p = 0.61	1.0 (0.75, 1.34) p = 0.97