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Article

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Low-Fat Dietary Pattern and Cancer Mortality in the Women's Health Initiative (WHI) Randomized Controlled Trial

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Abstract

Background: In the Women's Health Initiative Dietary Modification trial, a low-fat dietary pattern reduced deaths after breast cancer. Mortality from other cancer sites has not been reported.
Methods: A low-fat dietary pattern influence on deaths from and after site-specific cancers was examined during 8.5 years (median) of dietary intervention and cumulatively during 17.7 years (median) of follow-up. A total 48 835 postmenopausal women, ages 50–79 years, were randomly assigned from 1993 to 1998 at 40 US clinical centers to dietary intervention (40%, n = 19 541 or a usual diet comparison group (60%, n = 29 294). Dietary intervention influence on mortality from protocol-specified cancers (breast, colon and rectum, endometrium and ovary), individually and as a composite, represented the primary analyses.
Results: During the dietary intervention period, a reduction in deaths after breast cancer (HR = 0.65 95% CI = 0.45 to 0.94, $P = .02$) was the only statistically significant cancer mortality finding. During intervention, the HRs for deaths after the protocol-specified cancer composite were 0.90 (95% CI = 0.73 to 1.10) and 0.95 (95% CI = 0.85 to 1.06) for deaths after all cancers. During 17.7 years of follow-up with 3867 deaths after all cancers, reduction in deaths after breast cancer continued in the dietary intervention group (HR = 0.85, 95% CI = 0.74 to 0.99, $P = .03$). However, no dietary intervention influence on deaths from or after any other cancer or cancer composite was seen.
Conclusions: A low-fat dietary pattern reduced deaths after breast cancer. No reduction in mortality from or after any other cancer or cancer composite was seen.

In the Women's Health Initiative (WHI) Dietary Modification (DM) trial, 48 835 postmenopausal women were randomly assigned to a dietary modification group (40%, n = 19 541) or usual diet comparison group (60%, n = 29 294) to assess low-fat dietary pattern effects on breast cancer and colorectal cancer as co-primary endpoints. The dietary modification program reduced percent caloric intake from fat (mean [SD] to 24.3 [7.5]% from 35.1 [6.9]% at year 1), increased intake of fruit, vegetables, and grains (about 1 serving per day), and was associated with modest weight loss (2.9% loss after 1 year; −2.2 kg; $P < .001$) with differences between randomization groups maintained throughout the 8.5-year (median) dietary intervention period (1).

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At the protocol specified end of dietary intervention, although the breast cancer incidence was somewhat lower in the dietary intervention group, the difference was not statistically significant (HR = 0.91, 95% CI = 0.83 to 1.01, $P = .07$) and no effect on colorectal cancer incidence was seen (1,2). Subsequent analyses through 16.1 years of cumulative follow-up identified a statistically significant reduction in deaths after breast cancer measured from random assignment (HR = 0.82, 95% CI = 0.70 to 0.96, $P = 0.01$) (3) or measured from cancer diagnosis (HR = 0.78, 95% CI = 0.65 to 0.94, $P = .01$) (4). Dietary differences between randomization groups attenuated during the post-intervention period but remainde statistically significant (5).

The breast cancer findings prompted interest in examining the cumulative influence of the WHI dietary intervention on mortality from other cancers. Although information on the incidence of several other cancers has been reported (5–8), mortality information on individual cancers, including deaths from cancer and after cancer, have not been previously described. Therfore, we updated information on dietary intervention influence on breast cancer mortality and provide, for the first time, to our knowledge, similar information for select other cancers and cancer composite groups during 8.5 years (median) of dietary intervention and cumulatively throughout 17.7 years (median) of follow-up.

Methods

Participants

Details of the WHI DM trial, conducted at 40 US clinical centers with enrollment from 1993 through 1998, have been provided elsewhere (9). Eligible were postmenopausal women, ages 50–79 years, with no previous breast or colorectal cancer and with no other cancer in the 10 years prior to randomization, dietary fat intake greater than 32% of total energy by food frequency questionnaire (FFQ), a mammogram not suspicious for breast cancer, and anticipated survival of at least 3 years. The trial was approved by institutional review boards at the clinical centers and participants provided written informed consent.

Random Assignment

Participants were randomly assigned to a low-fat dietary pattern intervention group or a usual diet comparison group in a 40:60 ratio at a specified level of power, using a randomized permuted block algorithm, stratified by clinical center and age. The algorithm was developed and implemented electronically by the WHI Clinical Coordinating Center (Seattle, WA) (1).

Procedures

Baseline characteristics were collected by interview for medication use and by questionnaires for lifestyle and behavioral variables. Body weight, height, and waist circumference were measured, with body mass index (BMI (kg/m^2) calculated at baseline and annually during the dietary intervention. Mammography screening was biannually or annually for the 16% also participating in WHI hormone therapy trials. Colorectal cancer screening was not protocol mandated but screening information was collected. Physicians outside the WHI directed cancer therapy.

The low-fat dietary program was designed to reduce fat intake to 20% of total energy and increase vegetable, fruit, and grain intake (10). Calorie restriction or weight loss were not intervention targets. Dietary group participants received 18 group sessions led by centrally trained, registered dietitians/nutritionists in year one and quarterly maintenance sessions throughout the dietary intervention period. Comparison group participants received only written diet-related education materials. Participants provided a 4-day food record and a FFQ at baseline. Additional FFQs were obtained after 1 year and thereafter in a rotating subgroup sample yearly. Post-intervention findings are based on a subsample of single 24-hour dietary recalls for 1311 participants who reconsented four assessments between 2005 and 2010.

Outcome ascertainment was six monthly throughout the dietary intervention period. Dietary intervention ended after 8.5 years at the protocol-specified trial completion date of March 31, 2005. Subsequent outcome ascertainment required reconsent, obtained from 84.4% versus 81.1% of comparison and dietary group surviving participants, respectively, for follow-up through 2010 and 86.2% of surviving participants for subsequent, open-ended follow-up. National Death Index queries complete through September 2014 provided additional survival information regardless of reconsent status.

All cancers were confirmed after medical record review by clinical center physician adjudicators. Final adjudication and coding was performed at the WHI Clinical Coordinating Center. Cause of death was determined centrally by medical record or death certificate review and, in some cases, by participant relative report. All adjudicators were blind to randomization assignment.

Women with incident cancers continued to participate in subsequent dietary group meetings and activities (3). Thus, dietary group participants diagnosed with cancer shortly after randomization would have most nutritionist contacts after cancer diagnosis. In contrast, women diagnosed with cancer later in the dietary intervention period would have most nutritionist contacts before cancer diagnosis.

The protocol co-primary endpoints were incident invasive breast and colorectal cancer. The current analyses were not protocol mandated and represent secondary analyses. Ovarian and endometrial cancer also were identified as dietary targets in the original protocol (1), and the mortality outcomes for these four cancers individually and as a composite are the primary study outcomes in the current analyses. Secondary outcomes include mortality from a composite of “other cancers” (cancers not included in the primary analysis) and a composite of “total cancers.” Exploratory analyses examined mortality in lung cancer and pancreatic cancer (where the number of deaths was sufficient to support individual analyses). In addition, a composite of 13 cancer sites where the strength of evidence was judged sufficient to support an association between obesity and cancer risk by the World Cancer Research Fund/ International Agency for Research on Cancer (WCRF/IARC) including cancers of the esophagus (adenocarcinoma), gastric cardia, colon, rectum, liver, gallbladder, pancreas, breast, endometrial, ovaries, kidneys (renal-cell), meninges, thyroid, and multiple myeloma was also examined (11).

Statistical Analysis

The primary analysis endpoints of annualized rates of deaths from a specific cancer or cancer composite group and annualized rates of deaths after a specific cancer or cancer composite group are assessed by randomization group, during the dietary intervention period and cumulatively throughout all follow-up, by dividing the event number by the corresponding person-time

in each period. Hazard ratios, 95% confidence intervals, and *P* values were computed from Cox regression models stratified by age at random assignment, randomization status in the WHI hormone trials, and study period (time dependent). Definitions include deaths from cancer (cancer incidence followed by death attributed to the cancer) and deaths after cancer (cancer incidence followed by death from any cause). Analyses of deaths from and after specific cancers and the cancer composites include all 48 835 study participants measured from randomization. A CONSORT diagram outlining the flow of participants in the study through 16.5 years (median) follow-up has been recently published (3).

Because a previous analysis identified fewer deaths after breast cancer in dietary intervention group women with waist circumference greater than 88 cm (3), analyses in subgroups defined by BMI and waist circumference were investigated. Less than one statistically significant ($P \leq .05$) interaction would be expected by chance alone. All statistical tests were two-sided. Analyses used SAS 9.4 (SAS Institute, Cary, NC).

Results

Cancer risk factors including age, BMI, smoking status, alcohol consumption, menopausal hormone therapy use, weekly total energy expenditure, and 5-year breast cancer risk were not different between randomization groups (Table 1). Deaths from specific cancers and cancer composite groups during dietary intervention are presented by randomization group in Figure 1 (upper panel). As previously reported (3), fewer deaths from breast cancer were seen in the dietary intervention group during the intervention period (HR = 0.67, 95% CI = 0.43 to 1.06, $P = .08$), but the difference was not statistically significant. Although there were fewer deaths from endometrial cancer in the dietary intervention group, the number of deaths was limited (n = 22) and the finding was not statistically significant (HR = 0.70, 95% CI = 0.28 to 1.71, $P = .43$). For no other specific cancer or cancer composite group was a low-fat dietary pattern effect on death from cancer seen. Deaths after specific cancers and cancer composite groups during the dietary intervention period are presented in Figure 1 (lower panel). During intervention, the hazard ratios for deaths after the protocol-specified cancer composite were 0.90 (95% CI = 0.73 to 1.10) and 0.95 (95% CI = 0.85 to 1.06) for deaths after all cancers. As previously reported, the risk of death after breast cancer was lower in the dietary intervention group (annualized rates, 0.025% vs 0.038%, respectively, HR = 0.65, 95% CI = 0.45 to 0.94, $P = .02$). However, for no other specific cancer, cancer composite, or total cancer group was a low-fat dietary pattern effect on death after cancer seen. Of note, there was strong agreement between deaths from cancer and after cancer (upper vs lower panels) for HRs across all cancer sites.

Deaths from specific cancers and cancer composite groups throughout cumulative 17.7 years follow-up (N = 3437 deaths) by randomization group are presented in Figure 2 (upper panel). There were somewhat fewer deaths from breast and endometrial cancer in the intervention group, but the findings were not statistically significant. Deaths after specific cancers and cancer composite groups throughout cumulative follow-up (n = 3867) are presented in Figure 2 (lower panel). The risk of death after breast cancer continued to be lower in the intervention group (annualized rates, 0.098% vs 0.12%, HR = 0.85, 95% CI = 0.74 to 0.99, $P = .03$). However, for no other specific cancer or cancer composite group was a low-fat dietary pattern effect on death from or after cancer seen.

Due to the National Death Index search, death from cancer is more than 98% complete (13), whereas ascertainment of incident cancers after 2005 required consent for extended follow-up. Consequently, for some cancer sites, deaths from cancer exceeds deaths after specific cancers (eg, pancreatic cancer; Figure 2). However, a sensitivity analysis, moving the nonconsenting women into time-dependent strata wherein the outcome would be death from cancer, did not have an appreciable influence on results (Supplementary Figure 1, available online).

Cause of death is available for 3833 of 3867 cancer cases. Among the six specific cancer sites considered, lung cancer was the most common cause of death (16.9%, 648 deaths), followed by breast (7.5%, 289 deaths), pancreatic (7.3%, 280 deaths), colorectal (6.3%, 243 deaths), and ovarian cancers (5.7%, 218 deaths), with a smaller number from endometrial cancer (1.6%, 62 deaths). Deaths from cardiovascular disease were relatively common (9.4%, 360 deaths), and death from other cancers accounted for 32.6% of deaths.

In subgroup analyses, deaths after cancer for specific cancers and cancer composite groups throughout the cumulative follow-up period for BMI and waist circumference are presented in Figures 3 and 4, respectively. Differential influence of the dietary intervention on the composite endpoint of "other cancers" was observed with HR = 0.88 (95% CI = 0.78 to 0.99) and HR = 1.08 (95% CI = 0.97 to 1.20) among those with waist circumference less than 88 and 88 cm or greater, respectively ($P_{interaction} = .01$) (Figure 4). Additional sensitivity analyses, stratified by prior estrogen plus progestin or estrogen alone use, did not suggest that the influence of the dietary intervention could have been obfuscated by prior hormone use (Supplementary Figures 2 and 3, available online); $P_{interaction}$ across all endpoints were not statistically significant.

Discussion

With additional long-term follow-up of the WHI DM trial participants, deaths after breast cancer continued to be reduced in the dietary intervention group throughout 17.7 years of cumulative follow-up. However, in no other cancers, considered individually or as prespecified composites, was a dietary intervention influence on death from or death after cancer seen.

Although obesity and dietary fat intake may be thought to have similar influence on cancer incidence, in fact, evidence regarding the association of obesity, as compared with dietary fat intake, with specific cancer risks differs substantially (11,14,15). The recent WCRF/IARC working group identified 13 cancers where the evidence was judged sufficient to support association of obesity and cancer (11). In contrast, evidence regarding dietary fat intake as a cancer risk factor is limited as outlined below.

When the WHI DM trial was planned, breast cancer and colorectal cancer incidence were identified as co-primary endpoints with endometrial cancer and ovarian cancer also identified as potential responding sites (1). Recent observational studies examining dietary fat intake and cancer incidence provide some support for ovarian cancer benefit (16), mixed results for breast cancer (17) and pancreatic cancer (18), and largely neutral results for colorectal cancer (19) and endometrial cancer (12) with ongoing controversy over validity of dietary intake methodology (20). Of note, in their seminal report, Armstrong and Doll (21) found dietary fat intake most strongly correlated with breast cancer mortality, whereas other cancers were more strongly associated with meat consumption. In any event, the

Table 1. Baseline characteristics by randomization group (n = 48 835)

Characteristic	Intervention (n = 19 541) No. (%)	Comparison (n = 29 294) No. (%)	P
Age group at screening, y			.99
50–59	7206 (36.9)	10 792 (36.8)	
60–69	9083 (46.5)	13 632 (46.5)	
70–79	3252 (16.6)	4870 (16.6)	
Race/ethnicity			.74
White	15 871 (81.2)	23 891 (81.6)	
Black	2135 (10.9)	3127 (10.7)	
Hispanic	751 (3.8)	1094 (3.7)	
American Indian	88 (0.5)	114 (0.4)	
Asian/Pacific Islander	431 (2.2)	674 (2.3)	
Unknown	265 (1.4)	394 (1.3)	
Education			.65
≤High school/GED	4267 (22.0)	6468 (22.2)	
School after high school	7712 (39.7)	11 597 (39.8)	
College degree or higher	7446 (38.3)	11 044 (37.9)	
Marital status			.48
Never married	807 (4.1)	1163 (4.0)	
Divorced/separated	3128 (16.1)	4577 (15.7)	
Widowed	3029 (15.6)	4618 (15.8)	
Presently married/living as married	12 489 (64.2)	18 806 (64.5)	
Self-reported health			.35
Excellent	3115 (16.0)	4499 (15.4)	
Very good	7947 (40.9)	12 022 (41.2)	
Good	6798 (35.0)	10 282 (35.3)	
Fair/poor	1564 (8.1)	2351 (8.1)	
Time since menopause, y			.49
<10	6303 (34.8)	9362 (34.4)	
10 – <20	6737 (37.2)	10 081 (37.1)	
≥20	5065 (28.0)	7740 (28.5)	
Body mass index kg/m^2			.69
<25	5072 (26.1)	7587 (26.0)	
25 – <30	6944 (35.7)	10 452 (35.8)	
30 – <35	4451 (22.9)	6748 (23.1)	
≥35	2991 (15.4)	4377 (15.0)	
Smoking status			.23
Never	9918 (51.4)	15 029 (51.9)	
Past	8121 (42.1)	11 979 (41.3)	
Current	1273 (6.6)	1977 (6.8)	
Alcohol consumption			.74
Nondrinker	5441 (28.1)	8222 (28.3)	
≤1 drink/d	12 052 (62.2)	18 105 (62.2)	
>1 drink/d	1881 (9.7)	2767 (9.5)	
Treated diabetes (pills or shots)	866 (4.4)	1337 (4.6)	.49
Age at menarche, y			.93
<12	4313 (22.1)	6465 (22.1)	
12 – <14	10 815 (55.5)	16 166 (55.4)	
≥14	4355 (22.4)	6567 (22.5)	
Number of term pregnancies			.58
Never/no term pregnancy	2123 (10.9)	3227 (11.1)	
1	1682 (8.7)	2463 (8.4)	
2	4766 (24.5)	7002 (24.0)	
3	4714 (24.2)	7183 (24.6)	
≥4	6159 (31.7)	9294 (31.9)	
Number first-degree female relatives breast cancer			.30
0	15 657 (85.6)	23 542 (85.9)	
≥1	2641 (14.4)	3860 (14.1)	
Bilateral oophorectomy	3884 (20.3)	5997 (20.9)	.12
Unopposed estrogen use status			.72
Never used	12 277 (62.9)	18 477 (63.1)	
Past user	2295 (11.8)	3372 (11.5)	
Current user	4954 (25.4)	7419 (25.3)	

(continued)

Table 1. (continued)

Characteristic	Intervention (n = 19 541) No. (%)	Comparison (n = 29 294) No. (%)	P
Estrogen + progesterone use status			.75
Never used	14 193 (72.7)	21 298 (72.7)	
Past user	1656 (8.5)	2429 (8.3)	
Current user	3685 (18.9)	5560 (19.0)	
Baseline characteristics, mean (SD)			
Age at screening, y	62.3 (6.9)	62.3 (6.9)	.99
Physical functioning, RAND36	81.1 (19.3)	80.9 (19.5)	.27
Total energy expenditure/wk from phys act, MET-hours	10.0 (11.7)	10.1 (12.0)	.44
Body mass index, kg/m^2, baseline	29.1 (5.9)	29.1 (5.9)	.53
Gail 5-year risk	1.7 (0.9)	1.7 (1.0)	>.99

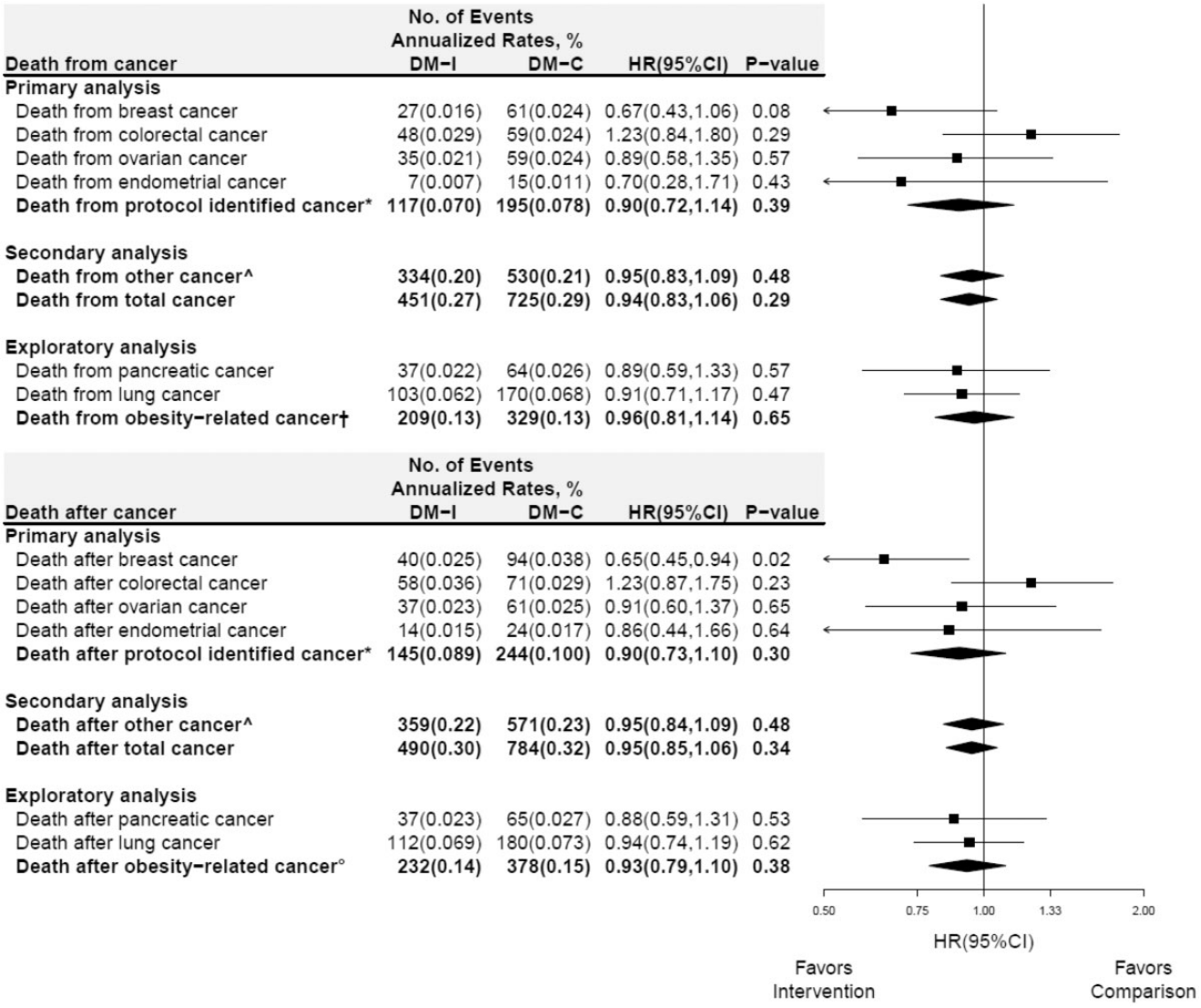

Figure 1. Death from and after select cancers in the Women's Health Initiative dietary modification trial during the 8.5-year (median) dietary intervention period. Forest plot and summary statistics of the dietary intervention's influence on deaths from (directly attributed to) cancer (upper panel) and deaths (from any cause) after cancer (lower panel). The P value corresponds to a two-sided score (log-rank) test. Percentages are annualized. *Protocol identified cancer includes: breast, colorectal, ovarian, and endometrial cancer. ^Includes cancers that were not identified in the protocol. †Includes deaths from cancers of the esophagus, stomach, colon, rectum, liver, gallbladder, pancreas, breast, endometrium, ovaries, kidneys, meninges, thyroid, or multiple myeloma. °Includes deaths from any cause after cancers of the esophagus (adenocarcinoma), gastric cardia, colon, rectum, liver, gallbladder, pancreas, breast, endometrium, ovaries, kidneys (renal-cell), meninges, thyroid and multiple myeloma. List of incident cancers based on (12). HR = hazard ratio; CI = confidence interval.

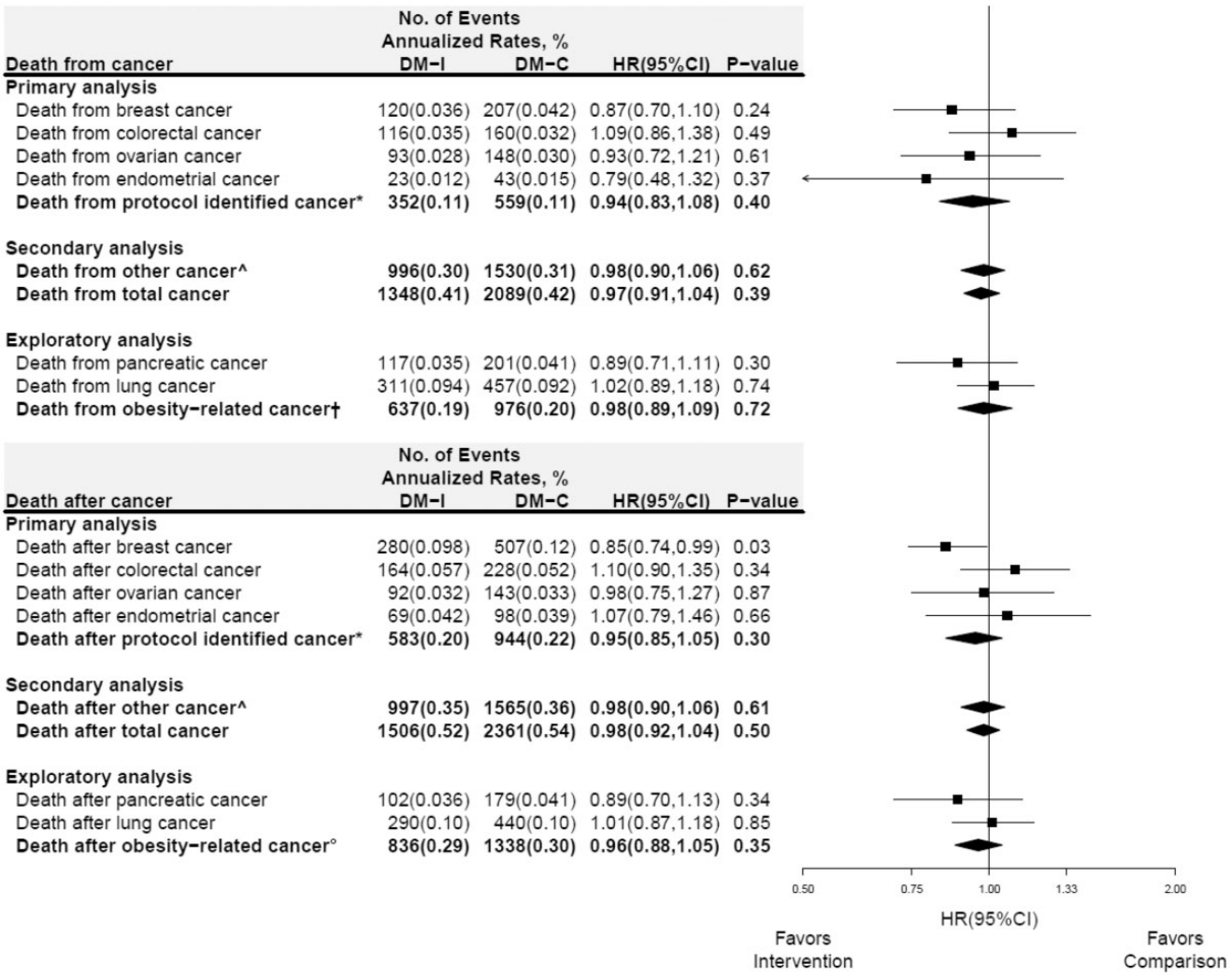

Figure 2. Death from and after select cancers in the Women's Health Initiative dietary modification trial during 17.7 years (median) of cumulative follow-up (intervention + postintervention periods; randomization through 30SEP2014). Forest plot and summary statistics of the dietary intervention's influence on deaths from (directly attributed to) cancer (upper panel) and deaths (from any cause) after cancer (lower panel). Ascertainment of incident cancer information after the intervention period ended required consent for extended follow-up. Consequently, the follow-up of nonconsenting women who did experience a cancer is censored in the analysis of death after cancer (lower panel). The *P* value corresponds to a two-sided score (log-rank) test. Percentages are annualized. See above for definition of: *protocol identified cancer; ^other cancer; †deaths from obesity-related cancer; and °deaths from any cause after incident obesity-related cancer. HR = hazard ratio; CI = confidence interval.

findings from the WHI DM randomized trial where multi-year, sustained differences in dietary intake, including reduction in total and animal fat, were maintained in the dietary intervention group compared with the usual diet group (1,3,4,7) have substantial strengths compared with findings from observational studies commonly based on a single dietary intake assessment.

For the specific question of dietary fat intake and survival following a breast cancer diagnosis, observational studies are limited (14) and provide inconsistent results (22,23). The current randomized clinical trial results indicate adoption of a low-fat dietary pattern reduces risk of deaths after breast cancer, a finding likely influenced by favorable effects on not only breast cancer but also other causes of mortality (3,4,24,25) as well as with improvement in physical functioning, general health, vitality, and self-rated health (26).

The effect of a low-fat dietary pattern to exclusively influence breast cancer may reflect the role of progestins as drivers of short- and long-term breast cancer progression. As previously reported (1,3), there was a statistically significant reduction in poor prognosis, estrogen receptor positive but progesterone receptor negative breast cancers (27) in the dietary intervention group, a finding that explained 29% of the difference in deaths after breast cancer between randomized groups (4). The potential role of progestin and other sex hormones seems plausible because the dietary intervention changed levels of circulating hormones including estradiol and sex hormone−binding globulin (1). Of note, the benefit in breast cancer survival due to reduction of circulating estrogens has been long known for aromatase inhibitors (28).

The potential role of progestins as drivers of breast cancer progression are supported by findings from the two WHI randomized hormone therapy trials. In these trials, breast cancer risk and mortality were persistently increased with estrogen plus progestin use and persistently decreased with estrogen alone use (29). In terms of mediating mechanisms, in preclinical studies, medroxyprogesterone acetate (the progestin used in the WHI hormone therapy trials), acting as a glucocorticoid,

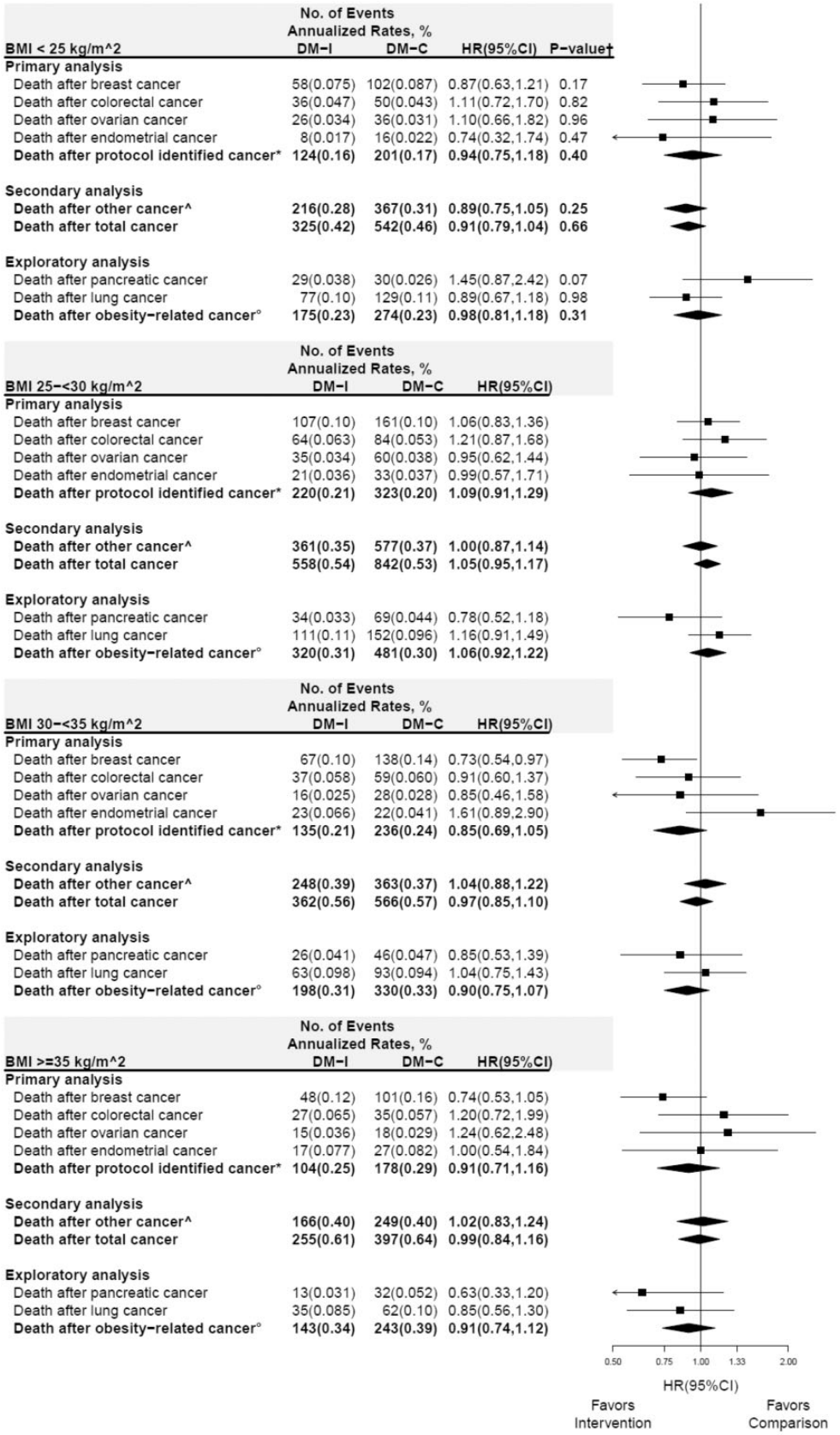

Figure 3. Subgroup analysis of deaths from any cause after cancer for cumulative follow-up (intervention period + postintervention periods) according to baseline body mass index (BMI) group. Forest plot and summary statistics of the dietary modification influence on deaths among normal (BMI < 25 kg/m^2; top panel), overweight (25–<30 kg/m^2), obese (30–<35 kg/m^2), and very obese women (≥35 kg/m^2; bottom panel). *P* value corresponds to a 1 degree-of-freedom test for trend of the interaction between BMI group and randomization group. See above for definition of: *protocol identified cancer; ^other cancer; and °deaths from any cause after incident obesity-related cancer. HR = hazard ratio; CI = confidence interval.

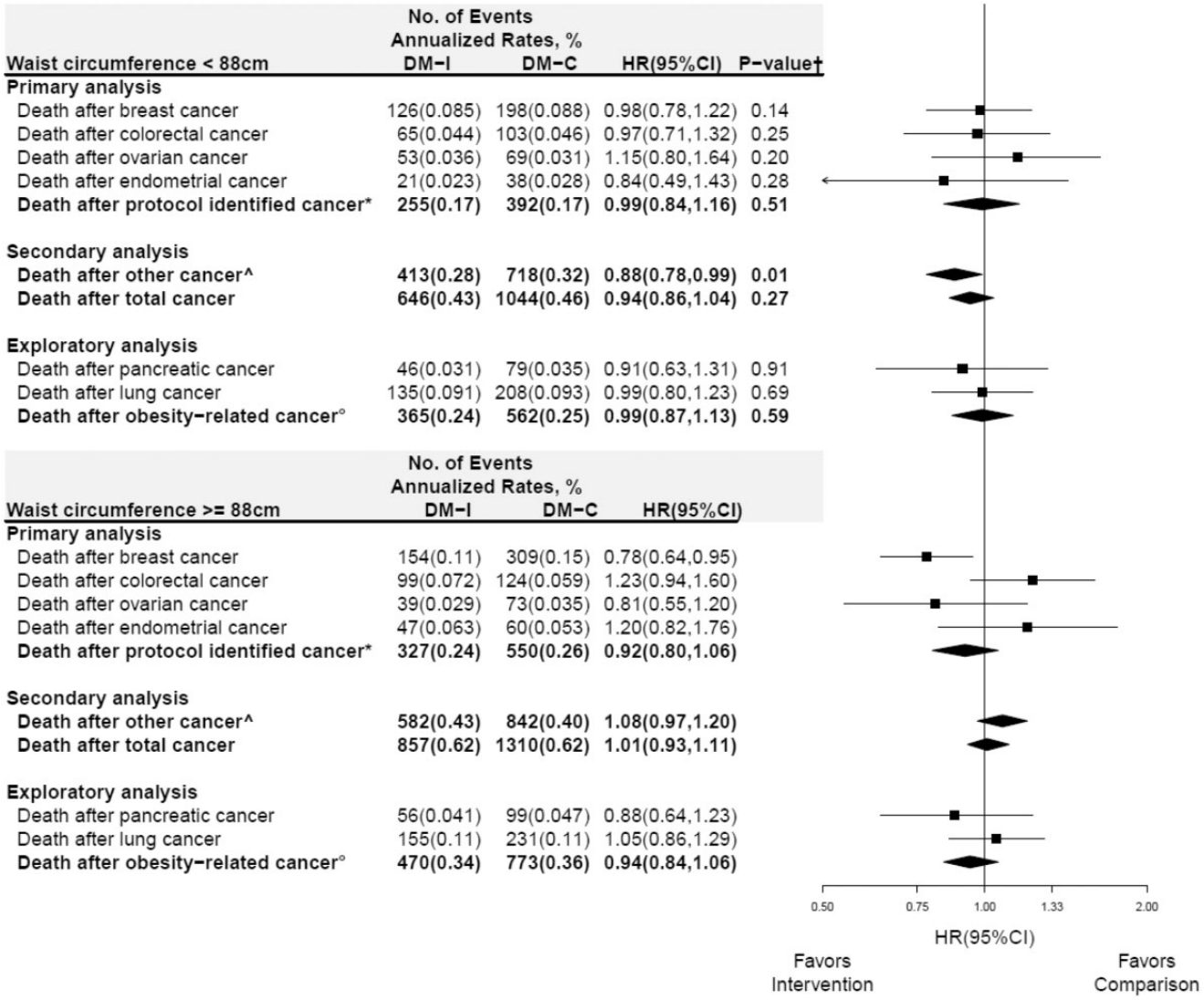

Figure 4. Subgroup analysis of deaths from any cause after cancer for cumulative follow-up (intervention period + postintervention periods) according to baseline waist circumference group. Forest plot and summary statistics of the dietary modification influence on deaths by waist circumference (<88 cm, top panel; vs ≥88 cm, bottom panel). P value corresponds to a test of the interaction between waist circumference group and randomization group. See above for definition of: *protocol identified cancer; other cancer; and ^deaths from any cause after incident obesity-related cancer. HR = hazard ratio; CI = confidence interval.

blunts estrogen-induced apoptosis leading to mammary epithelial proliferation (30). In addition, long-term stimulation of breast cancer risk likely reflects progestin's role in expanding stem/progenitor cell numbers (31). To our review, a similar role for progestins in other cancers has not been described.

In subgroup analyses, the previously reported (3) effect modification on death after breast cancer by waist circumference diminished and was no longer statistically significant (Figure 4). Although waist circumference was also associated with outcome of the composite "other cancers" (Figure 4), this finding was likely due to chance because the main effect of this secondary endpoint was not statistically significant.

In an exploratory analysis, no effect of the low-fat dietary pattern on a composite of 13 obesity-associated cancer sites (11) was seen. Perhaps this finding should not be surprising because the current intervention targeted dietary fat intake and diet composition rather than weight loss. In addition, adjustment for weight loss did not alter the reduction in deaths after breast cancer result (4). With respect to obesity, although the substantial, 20-kg weight loss seen in bariatric surgery populations has been associated with lower cancer risk (32), influence of lesser weight loss commonly achievable without surgery on cancer risk has not been convincingly demonstrated (11). Thus, the magnitude of the weight loss seen in the current study may have been insufficient to influence other obesity-associated cancers.

Study strengths include the randomized design, a population of 48 835 postmenopausal women, 3867 deaths after cancer, dietary program adherence supported by previously published (1) measured body weight and biomarker differences between randomization groups, serial screening mammography, verified cancer diagnoses, and long follow-up. Study limitations include those associated with secondary analyses and limited cancer therapy information. Because the trial was powered for dietary influence on breast cancer incidence, power is limited for cancers with lower incidence.

Although the findings of dietary intervention influence on deaths after breast cancer represent a secondary analysis in a randomized clinical trial, the absolute benefit in breast cancer overall survival seen is comparable to that with adjuvant anthracycline and taxane use (33), aromatase inhibitor benefit over tamoxifen in postmenopausal women (34), and is somewhat lower than trastuzumab addition to chemotherapy benefit for human epidermal growth factor receptor 2 positive breast cancer (35).

We have described the WHI dietary intervention as requiring a modest reduction in fat intake with minimal weight loss as achievable by many (3) where subgroup analyses suggest benefit in women with obesity or abdominal circumference greater than 88 cm (as marker of central obesity) (3,4). In this setting, referral to trained nutritionists, presented as obesity management, would likely be reimbursable by Medicare and other providers. Alternatively, centrally mediated programs for implementation of low-fat dietary regimens have been developed (36,37), which provides an even lower cost option for broad implementation.

The current breast cancer findings are generally supportive of the WCRF/AICR cancer prevention recommendations that include limiting "fast foods" and red and processed meat and and incorporating whole grains and fruits and vegetables (38). However, because only breast cancer outcome was affected by the WHI dietary intervention, other obesity-related cancers may require different intervention strategies. In summary, after long-term follow-up, women randomly assigned to a low-fat dietary pattern had a reduced risk of death after breast cancer. In no other cancer or cancer composite group was a dietary intervention effect on death from or after cancer seen.

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Contributors: RTC wrote the analysis proposal and initial draft of the report. Authors RTC, AKA, GLA, and RLP had full access to the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. AKA and RLP were responsible for the statistical analysis. RTC, AKA, CAT, GLA, JEM, MSS, BVH, TER, LS, DL, WB, MV, CW, LQ, LH, FT, and RLP provided critical review of the manuscript for important intellectual content. RTC, JEM, MLS, MSS, BVH, KCJ, JW, MJO, and RLP collected the data and obtained study funding.

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Additional information: A full list of all the investigators who have contributed to Women's Health Initiative science appears at: https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Inv estigator%20Long%20List.p.

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