Low-Fat Dietary Pattern and Cancer Incidence in the Women's Health Initiative Dietary Modification Randomized Controlled Trial

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Background The Women's Health Initiative Dietary Modification (DM) Randomized Controlled Trial evaluated the effects of a low-fat dietary pattern on chronic disease incidence, with breast cancer and colorectal cancer as primary outcomes. The trial protocol also listed ovarian cancer and endometrial cancer as outcomes that may be favorably affected by the intervention.

Methods A total of 48 835 postmenopausal women were randomly assigned during 1993–1998 to a DM intervention (n = 19 541) or comparison (usual diet; n = 29 294) group and followed up for an average of 8.1 years. The intervention goal was to reduce total fat intake to 20% of energy and to increase consumption of vegetables, fruits, and grains. Cancer outcomes were verified by pathology report review. We used weighted log-rank tests to compare incidence of invasive cancers of the ovary and endometrium, total invasive cancer, and invasive cancers at other sites between the groups. All statistical tests were two-sided.

Results Ovarian cancer risk was lower in the intervention than in the comparison group ($P = .03$). Although the overall ovarian cancer hazard ratio (HR) was not statistically significantly less than 1.0, the hazard ratio decreased with increasing intervention duration ($P_{trend} = .01$). For the first 4 years, the risk for ovarian cancer was similar in the intervention and control groups (0.52 cases per 1000 person-years in the intervention group versus 0.45 per 1000 person-years in the comparison group; HR = 1.16, 95% confidence interval [CI] = 0.73 to 1.84); over the next 4.1 years, the risk was lower in the intervention group (0.38 cases per 1000 person-years in the intervention group versus 0.64 per 1000 person-years in the comparison group; HR = 0.60, 95% CI = 0.38 to 0.96). Risk of cancer of the endometrium did not differ between the groups ($P = .18$). The estimated risk of total invasive cancer was slightly lower in the intervention group than in the control group (HR = 0.95, 95% CI = 0.89 to 1.01; $P = .10$).

Conclusions A low-fat dietary pattern may reduce the incidence of ovarian cancer among postmenopausal women.

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The Women's Health Initiative (WHI) was initiated in 1992 (1) and included a full-scale randomized controlled trial of a dietary modification (DM) intervention with the goals of reduced fat intake (≤20% of energy from fat) and increased intake of vegetables and fruit (≥5 servings/day) and grains (≥6 servings/day). A total of 48 835 postmenopausal women aged 50–79 years were enrolled, of whom 19 541 (40%) were randomly assigned to the low-fat "dietary pattern" (intervention group) and 29 294 (60%) were assigned to continue their usual diet (comparison group). The DM trial was designed to test whether a low-fat dietary pattern could reduce the risk of cancer among postmenopausal women, with breast and colorectal cancers listed as primary outcomes. Based on favorable plasma cholesterol effects of the DM in preceding feasibility studies (2), coronary heart disease was listed as a secondary outcome.

Results for the designated primary and secondary outcomes were recently reported (3–5). For breast cancer (3), the hazard ratio (HR) for the intervention versus comparison group was 0.91 (95%

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confidence interval [CI] = 0.83 to 1.01). The 9% lower incidence seen in the intervention group was similar to that projected under study design assumptions, given the measured dietary differences between randomization groups. In addition, there was a statistically significant interaction ($P_{interaction}$ = .04) between baseline percent energy from fat and breast cancer risk, with women in the upper quartile of percent energy from fat at baseline (>36.8% of total energy from fat) having a larger estimated reduction in risk with the intervention (HR = 0.78, 95% CI = 0.64 to 0.95). By contrast, the hazard ratio for colorectal cancer in the intervention versus comparison group was 1.08 (95% CI = 0.90 to 1.29), with no suggestion of intervention benefit (3).

The study protocol also listed the ovary and the endometrium as cancer sites that would potentially benefit from the DM intervention, in part based on international correlation analyses (6,7). Analytic epidemiologic studies also tend to support associations between reduced fat intake and reduced risk of these cancers. For example, the 1997 international review of food, nutrition, and the prevention of cancer (8) stated that "overall, the evidence suggests that diets high in total fat may increase the risk of ovarian cancer but is, as yet, insufficient," with a nearly identical statement for endometrial cancer. For ovarian cancer, more recent studies (9–14) provide mixed findings. Recent analytic epidemiology studies of endometrial cancer include some reports of positive associations with dietary fat, particularly among obese women (15,16), but those also leave the question of association unresolved.

Observational studies are also inconclusive concerning the association between dietary fat and cancers of sites other than breast, colon, rectum, ovary, or endometrium. For example, the international review (8) lists lung cancer as possibly related to total dietary fat but does not list any cancer as "convincingly" or "probably" related to dietary fat. International correlation analyses, by contrast, have suggested positive associations of dietary fat with several cancers, including cancers of the kidney, bladder, and lung (6,8), but have only hypothesis generation potential.

In this study, we compared cancer incidence rates through the end of the DM trial intervention period for invasive cancers of the ovary and endometrium. We also evaluated the DM intervention in relation to total and site-specific invasive cancer.

Subjects and Methods

Detailed accounts of the methodology of the WHI DM trial have been presented (1,3–5). Briefly, participating women were postmenopausal and aged 50–79 years at recruitment during 1993–1998. Interested and eligible women could be randomly assigned to one or both of the DM trial and companion trials of postmenopausal hormone therapy and had the opportunity for further random assignment into a trial of calcium and vitamin D supplementation following 1 year of clinical trial participation. DM intervention and maintenance activities continued throughout the average 8.1-year average follow-up period (3), which concluded as planned on March 31, 2005. Major DM trial exclusions included any prior breast or colorectal cancer, other cancer except nonmelanoma skin cancer within the past 10 years, medical conditions yielding predicted survival of less than 3 years, adherence or retention concerns, or a baseline diet estimated to have less than 32% of energy from fat, as assessed by the WHI food-frequency questionnaire (FFQ).

CONTEXT AND CAVEATS

Prior knowledge

Previously, the Women's Health Initiative Dietary Modification (DM) trial analyzed whether a low-fat diet would alter the incidence of breast cancer, colorectal cancer, chronic disease, and cardiovascular disease.

Study design

Randomized controlled trial of postmenopausal women who were assigned to their usual diet or to the DM intervention. Risks of invasive ovarian and endometrial cancer as well as total invasive cancer and invasive cancer at other sites for a period of 8.1 years were determined.

Contributions

Risk for invasive ovarian cancer was similar in the two groups in the first 4 years but reduced in the subsequent 4.1 years among women in the intervention group compared with women in the comparison group. No statistically significant differences in risk were observed among the two groups for total invasive cancer or invasive endometrial cancer.

Implications

A low-fat diet may reduce the incidence of ovarian cancer in postmenopausal women.

Limitations

Adjustment for multiple comparisons for the risks for the five types of cancer targeted in the trial may reduce the statistical significance of the findings.

The 40% of women assigned to a low-fat dietary pattern received an intensive behavioral modification program to assist them in achieving the previously mentioned dietary intervention goals. The intervention program included 18 group sessions in the first year and quarterly maintenance sessions thereafter. In these sessions, groups of 8–15 women were led by specially trained and certified nutritionists. As elaborated in (1), each session included both nutritional topics (e.g., fat content of food, fat budgeting, high-risk food situations, and nutritional evaluation) and behavioral topics (e.g., dietary self-monitoring, social influences on eating, group cohesiveness, and relapse prevention). All participating women provided a 4-day food record at baseline and provided FFQs at baseline and 1 year and approximately every 3 years thereafter on a rotating basis, and randomly selected subsets provided 24-hour dietary recalls every 3 years.

As previously described (3–5), the dietary intervention resulted in noteworthy dietary differences between randomization groups as assessed by the WHI FFQ. In particular, the percentage of energy from fat was lower in the intervention group (versus the comparison group) by 10.7% at 1 year, 9.5% at 3 years, and 8.1% at 6 years. Consumption of vegetables and fruit was higher in the intervention group by 1.2, 1.3, and 1.1 servings at 1, 3, and 6 years from random assignment, respectively, and grain consumption was higher by 0.9, 0.7, and 0.4 servings at these times. Biomarker data (3–5) lend support to a meaningful dietary difference between intervention and control group women, including differences in blood estradiol and in certain blood micronutrient concentrations.

Participating women were queried twice per year regarding diagnosis of any cancer other than nonmelanoma skin cancers. Cancer screening behaviors, including mammograms (which were required at least every 2 years), pap smears, and colonoscopies, were tracked throughout the intervention period and did not differ substantially between randomization groups (3,4). Cancer reports were verified by medical record and pathology report review by centrally trained physician adjudicators at each of the 40 participating clinical centers (17). Central adjudication and coding at the clinical coordinating center using the National Cancer Institute's Surveillance, Epidemiology, and End Results coding system also took place for cancers of the breast, colon, rectum, ovary, and endometrium. For this report, 308 cancers of "other" sites classified as in situ or borderline concerning invasiveness were reviewed, along with 69 cancers having unknown tumor behavior. As a result of this review, which was conducted blinded to random assignment, 55 of these 377 cancers were classified as invasive on central review and are included in this report. Review of a small sample (n = 30) of "other" cancers classified locally as invasive provided reassurance that few invasive cancers would be reclassified as noninvasive on central review. As in previous reports, disease events are included through the final intervention visit for each participating woman, which was scheduled between October 1, 2004, and March 31, 2005.

Statistical Analysis

The statistical design and analysis methods have also been described previously (1,3). Disease incidence comparisons between the intervention and comparison groups are based on the intent-to-treat principle using time-to-event methods. A weighted log-rank test was prespecified in the WHI protocol as the primary means of comparing randomization groups in the clinical trial. For cancer outcomes, the weights were specified to increase linearly from zero at random assignment to a plateau of 1.0 at 10 or more years following enrollment. This weighting procedure was selected to increase statistical power under hypothesized intervention effects that were more pronounced toward the end of the intervention period. Overall hazard ratio estimates and nominal 95% confidence intervals from Cox regression (18) analyses are also presented. These estimates arise from proportional hazards models, and confidence intervals that exclude 1.0 correspond to unweighted log-rank tests that are statistically significant at the $\alpha = .05$ level. If the hazard rates for intervention and comparison groups are not proportional, the Cox model hazard ratio can be interpreted as estimating a type of averaged hazard ratio over the study follow-up period. Tests for time trends in hazard ratio over the intervention period were carried out by including a product term between randomization assignment and time from random assignment in the Cox regression procedure. All statistical tests were two-sided.

Analyses for ovarian cancer were restricted to women having at least one ovary at baseline. Analyses for endometrial cancer were restricted to women with a uterus at baseline. Interactions between hazard ratios and baseline factors (e.g., age, race/ethnicity, body mass index [BMI]) were examined by the inclusion of product terms between the randomization assignment and baseline factor categories in the Cox regression analysis. Interaction analyses with baseline dietary factor relied mostly on FFQ data. However, baseline FFQ percent energy from fat and total fat estimates were distorted for trial enrollees due to the use of the FFQ in eligibility screening. Hence, interactions with these factors used data from baseline 4-day food records. For reasons of cost, the 4-day food records were stored but not routinely analyzed in the trial cohort. The 4-day food records of ovarian cancer patients were analyzed for this report and were used in "patient-only" analyses to examine ovarian cancer hazard ratios according to baseline percentage energy from fat and total fat. This methodology was used also in earlier reports (3–5) from the DM trial. In the absence of a natural categorization (e.g., decade of age, major race/ethnicity, BMI categories), baseline factors were classified into quartiles, or into tertiles if the number of disease events was small (e.g., for ovarian cancer).

The Cox regression model was also used for explanatory analyses of intervention effects. For example, both an indicator variable for intervention group assignment and a time-dependent variable for body weight change from baseline to 1 year from random assignment were included in Cox model analyses (along with baseline weight) to examine whether weight changes attributable to the intervention provided an explanation for observed intervention effects on the hazard ratio.

The time to event for a particular outcome was defined as the number of days after randomization to the first diagnosis of the designated event (e.g., invasive cancer of any site). Follow-up time was censored at the time of a woman's last documented contact within the intervention period for the trial, or death. Ovarian cancers were classified according to disease stage and tumor histology using the National Cancer Institute's Surveillance, Epidemiology, and End Results coding system, with some grouping of rare histologic types.

From a multiple testing perspective, results for cancers of the ovary and endometrium can be viewed in the context of comparisons for each of the five "diet-related" cancers (breast, colon, rectum, ovary, and endometrium) specified in the DM trial protocol, and results for other cancers can be interpreted in the context of the entire set of approximately 25 site-specific comparisons. Statistical significance testing was based on the weighted log-rank test; trend testing and unweighted log-rank tests provided additional information about specific comparisons.

Results

Baseline Characteristics

The baseline characteristics of the 19 541 women in the intervention group and the 29 294 women in the comparison group have been described (3–5). Briefly, the average age of study participants was 62.3 years, 18.6% were of minority race/ethnicity, about three-quarters were overweight or obese (BMI $\geq$ 25 kg/m^2), and more than 40% reported a history of hypertension. The follow-up period ranged from 6 to more than 11 years and averaged 8.1 years.

Ovarian Cancer

We observed a lower incidence of ovarian cancer in the intervention group than in the comparison group ($P = .03$, from the protocol-specified weighted log-rank test) (Table 1) among the 39 954 women (n = 15 657 intervention, n = 23 297 comparison) without

Table 1. Comparison of incidence of invasive ovarian cancer, invasive endometrial cancer, and other invasive cancers between intervention and comparison groups in the Women's Health Initiative (WHI) Dietary Modification trial*

Cancer site	Incidence per 1000 person-years (No. of cases)			
	Intervention	Comparison	P†	HR (95% CI)‡
Ovary	0.36 (57)	0.43 (103)	.03	0.83 (0.60 to 1.14)
Endometrium	0.79 (125)	0.71 (170)	.18	1.11 (0.88 to 1.40)
Breast	4.15 (655)	4.52 (1072)	.09	0.91 (0.83 to 1.01)
Colorectal	1.27 (201)	1.18 (279)	.29	1.08 (0.90 to 1.29)
All other sites	4.56 (720)	4.81 (1140)	.30	0.95 (0.86 to 1.04)
Total cancer	10.69 (1687)	11.22 (2661)	.10	0.95 (0.89 to 1.01)

* Trial included 19541 women in the intervention group and 29294 women in the comparison group.

† Weighted log-rank test (two-sided) stratified by age (5-year categories) and randomization status in the WHI hormone therapy trials (active therapy, placebo, or nonparticipant, separately for women with or without a uterus). Weights increase linearly from zero at random assignment to a maximum of 1.0 at 10 years.

‡ HR = hazard ratio; CI = confidence interval, from a proportional hazards model stratified by age (5-year categories) and randomization status in the WHI hormone therapy trials.

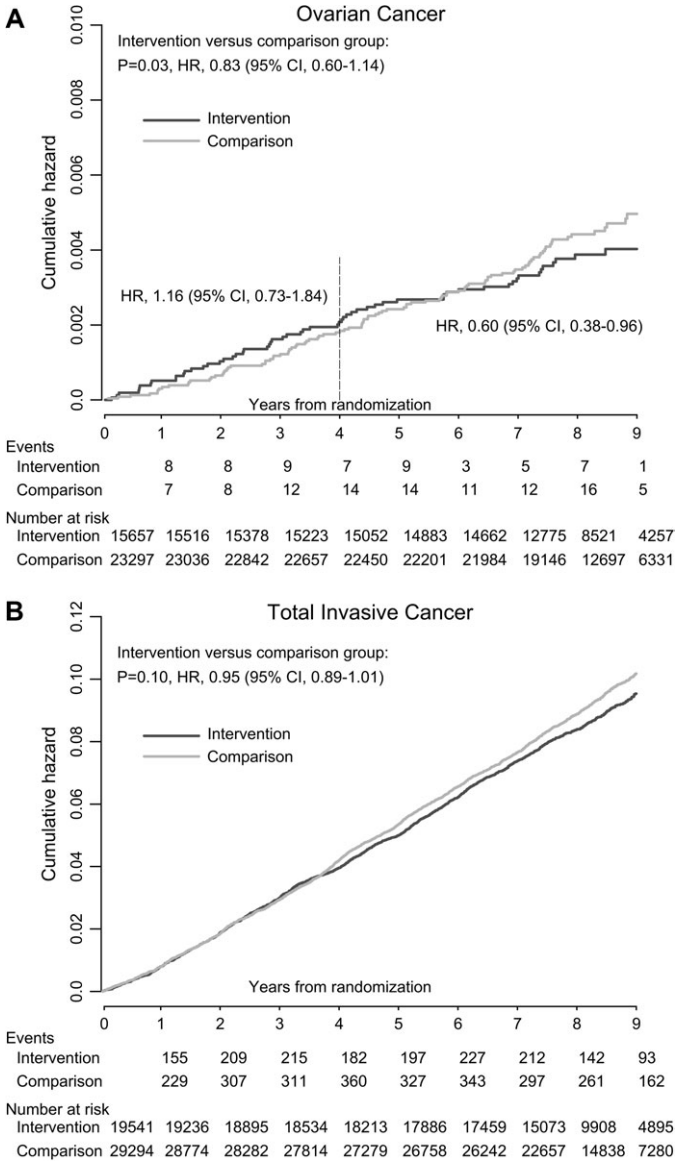

Fig. 1. Cumulative hazard estimates for invasive cancers in the intervention and comparison groups in the Women's Health Initiative Dietary Modification trial. **A)** Invasive ovarian cancer. **B)** Total invasive cancer. *P* = statistical significance level based on (two-sided) weighted log-rank test; HR = hazard ratio; CI = confidence interval. Hazard ratio (95% confidence interval) given for overall trial and separately for the first 4 years and subsequent years for ovarian cancer. The cumulative hazard plots were truncated at 9 years to avoid unstable estimates, thereby omitting the final four ovarian cancers (all in the comparison group).

prior bilateral oophorectomy at baseline. However, the hazard ratio averaged over the entire intervention period was not statistically significantly less than 1.0 (HR = 0.83, 95% CI = 0.60 to 1.14; unweighted log-rank *P* = .24) (Fig. 1, A). This apparent discrepancy can be explained by variation in this hazard ratio across the intervention period. Specifically, a test for trend in hazard ratio in relation to time from random assignment was statistically significant (P_{trend} = .01). Dividing the 8.1-year average trial follow-up period into the first 4 and latter 4.1 years yielded hazard ratios of 1.16 (95% CI = 0.73 to 1.84, *P* = .53) and 0.60 (95% CI = 0.38 to 0.96, *P* = .03), respectively. The absolute incidence rates in the first 4 years were 0.52 cases per 1000 person-years in the intervention group and 0.45 cases per 1000 person-years in the comparison group. The corresponding rates in the subsequent years were 0.38 and 0.64 in the intervention and comparison groups, respectively. Hence, although there was little evidence for an intervention effect on ovarian cancer risk during the first few intervention years, a stronger and nominally statistically significant risk reduction emerged in the later years. Rates of bilateral oopherectomy during follow-up did not differ between randomization groups (*P* = .53), and the weighted log-rank test for the difference in incidence between the intervention and comparison groups remained statistically significant (*P* = .04) when the follow-up period was censored at the date of surgery for women undergoing bilateral oophorectomy during trial follow-up.

We also examined the distribution of tumor histologic type and disease stage among women who developed invasive ovarian cancer (Table 2). The numbers of women in each category were small, but there did not appear to be any noteworthy differences in stage distribution between the intervention and comparison groups within major tumor histology categories.

Endometrial Cancer

The overall incidence of cancer of the endometrium did not differ between randomization groups (HR = 1.11, 95% CI = 0.88 to 1.40; *P* = .18), based on 27 629 women (n = 11 092 intervention, n = 16 537 comparison) with a uterus at baseline. No indication of an intervention effect later in the intervention period was observed. Hysterectomy rates did not differ between randomization groups during follow-up (*P* = .85), and results were unchanged by additionally censoring follow-up times at the date of hysterectomy.

Breast, Colorectal, and All Invasive Cancers

The incidence of breast and colorectal cancers in the intervention and comparison groups was previously reported (3–4) and is given in Table 1, as is the incidence of invasive cancer at sites other than

Table 2. Stage and histology distribution of ovarian cancer patients by randomization group in the Women's Health Initiative Dietary Modification trial*

SEER* stage	Tumor histology, no. of patients (%)							
	Carcinoma		Endometrial		Serous		Other	
	I*	C*	I	C	I	C	I†	C‡
Localized	1 (9)	0 (0)	1 (20)	5 (33)	1 (4)	2 (4)	1 (17)	3 (33)
Regional	0 (0)	1 (8)	2 (40)	4 (27)	5 (18)	6 (12)	4 (67)	1 (11)
Distant	10 (91)	12 (92)	2 (40)	6 (40)	22 (79)	41 (84)	1 (17)	5 (56)
Total	11	13	5	15	28	49	6	9

* Twenty-three patients who were identified by death report only (7 intervention, 17 comparison, and one intervention with missing stage) were excluded. SEER = Surveillance, Epidemiology, and End Results Program of the National Cancer Institute; I = intervention group; C = comparison group.

† Included one localized and one regional clear cell; one mucinous regional, one regional, and one distant mixed mullerian; and one regional Brennan tumor.

‡ Included two localized and three distant clear cell; one localized, one regional, and one distant mucinous; and one distant signet ring cell tumor.

breast, colorectum, ovary, and endometrium. The hazard ratio for total (invasive) cancer was 0.95 (95% CI = 0.89 to 1.01), suggestive of an intervention benefit. The statistical significance level for the total cancer comparison was $P = .10$ (both weighted and unweighted log-rank tests). No suggestion was observed of a trend in hazard ratio for total cancer incidence with time from random assignment (Fig. 1, B; $P_{trend} = .68$). For completeness, we note that hazard ratios for total cancer exclusive of breast cancer (HR = 0.96, 95% CI = 0.88 to 1.05) and for total cancer exclusive of colorectal cancer (HR = 0.94, 95% CI = 0.88 to 1.00; $P = .05$) were similar to that shown in Table 1 for total cancer.

Ovarian and Total Invasive Cancer Risk According to Baseline Characteristics

We next examined variations in the overall hazard ratio for ovarian cancer according to the baseline characteristics of participating women and to baseline dietary variables relevant to the DM intervention (Table 3). Interactions of hazard ratios with baseline percentage of energy from fat ($P = .05$) and baseline total fat intake ($P = .06$) were suggested. Among women whose values fell in the upper tertile for these variables, based on their baseline 4-day food records, estimated intervention versus comparison group hazard ratios (and 95% confidence intervals) over the entire follow-up period were 0.58 (95% CI = 0.31 to 1.08) for percentage of energy from fat and 0.49 (95% CI = 0.25 to 0.93) for total fat.

Hazard ratio interaction analyses were also performed for total cancer (Table 4). No interactions were statistically significant, although there was a suggestion ($P = .07$) of a lower hazard ratio among women with a personal history of cancer (other than nonmelanoma skin cancer) before trial enrollment. Among these women, the hazard ratio was 0.74 (95% CI = 0.57 to 0.98).

Weight Change in Relation to Ovarian and Total Invasive Cancer Effects

The major emphasis of the DM intervention was on dietary fat reduction, with less emphasis placed on increasing intake of vegetables, fruits, and grains (4). The DM intervention did not target a reduction in total calories, although the intervention group did experience an early modest weight loss, with an average weight difference between randomization groups of 1.9 kg at 1 year from random assignment that diminished to 0.4 kg at 7.5 years (19). To test for a role of weight loss in explaining the observed hazard ratio trends, the hazard ratios for ovarian cancer and total cancer risk in the intervention versus comparison groups were recalculated in Cox model analyses that included both baseline weight and weight change from baseline to 1 year as a time-dependent covariate. The resulting overall intervention versus comparison group hazard ratios were 0.79 (95% CI = 0.55 to 1.13) for ovarian cancer and 0.95 (95% CI = 0.89 to 1.02) for total cancer, similar to the hazard ratio values given in Table 1 from the corresponding analyses without the weight and weight change variables. Thus, for these clinical outcomes, it is likely that any observed differences in disease incidence rates between intervention and comparison groups primarily reflect differences in percentage of energy obtained from fat.

Other Cancer Sites

The "all other sites" category of Table 1 was divided according to anatomic site (Table 5). Even categories with few incident events were included for completeness. The statistical significance level for Hodgkin disease was $P = .05$, based on only nine patients. Otherwise, none of the sites listed had a weighted log-rank P value less than or equal to .05, and none of the 95% confidence intervals excluded 1.0, although unweighted log-rank P values (not shown) were .06 for biliary tract cancer and .08 for liver cancer.

Discussion

This report provides evidence for a reduced risk of ovarian cancer as a result of the low-fat dietary pattern intervention, along with suggestive evidence for a reduction in total invasive cancer. However, several issues need to be considered in interpreting these findings. Ovarian cancer was one of five DM protocol-specified cancers tested. The probability that a statistical significance level as extreme as the observed weighted log-rank $P = .03$ arises by chance when five tests are conducted could be as large as 15% using a conservative Bonferroni correction. Also, the lack of a consistent effect across the entire intervention period may detract from the certainty of an intervention effect. Furthermore, there is a possibility that the cumulative hazard estimates shown in Fig. 1 could be distorted if ovarian cancers were detected earlier in the intervention group than in the comparison group.

The following points can be made in response to these issues and in support of an ovarian cancer risk reduction as a result of the intervention. Concerning the possibility of early detection in the intervention group, we note that the evidence for an early elevation in risk is weak. For example, a test of hazard ratio equal to 1.0 during the first 4 intervention years is not statistically significant ($P = .53$). Also, earlier detection would have given rise to a cumulative hazard curve for the intervention group that was elevated early in the intervention period and converged to that for the comparison group some years later, a pattern quite different from the crossing cumulative hazard curves shown in Fig. 1. Finally, the distribution of ovarian cancer diagnosis by stage and histology (Table 2) does not suggest any important differential ascertainment.

Table 3. Women's Health Initiative Dietary Modification trial intervention versus comparison group hazard ratios (HRs) and 95% confidence intervals (CIs) for invasive ovarian cancer by baseline characteristics and dietary factors

Variable	Incidence per 1000 person-years (No. of cases)		HR (95% CI)*	$P_{interaction}$
	Intervention (N = 57)	Comparison (N = 103)		
Age at screening, y				.18
50–59	0.26 (16)	0.37 (34)	0.70 (0.39 to 1.27)	
60–69	0.32 (23)	0.49 (53)	0.65 (0.40 to 1.05)	
70–79	0.72 (18)	0.42 (16)	1.69 (0.86 to 3.31)	
Race/ethnicity				.58
White	0.39 (50)	0.47 (91)	0.82 (0.58 to 1.16)	
Black	0.24 (4)	0.16 (4)	1.40 (0.35 to 5.62)	
Hispanic	0.35 (2)	0.24 (2)	1.45 (0.20 to 10.32)	
Asian/Pacific Islander	0 (0)	0.76 (4)	–	
American Indian	0 (0)	1.13 (1)	–	
Other	0.51 (1)	0.32 (1)	1.48 (0.09 to 24.32)	
Family history of ovarian or breast cancer†				.27
Yes	0.56 (17)	0.47 (21)	1.16 (0.61 to 2.20)	
No	0.32 (39)	0.43 (78)	0.75 (0.51 to 1.11)	
History of oral contraceptive use				.56
Yes	0.29 (20)	0.38 (41)	0.74 (0.44 to 1.27)	
No	0.43 (37)	0.48 (62)	0.89 (0.59 to 1.34)	
Diabetes‡				.48
Yes	0.15 (1)	0.40 (4)	0.36 (0.04 to 3.22)	
No	0.37 (56)	0.44 (99)	0.84 (0.61 to1.17)	
Body mass index, kg/m^2				.54
<25.9	0.42 (22)	0.42 (33)	1.01 (0.59 to 1.73)	
25.9 to <30.9	0.30 (16)	0.50 (40)	0.60 (0.34 to 1.07)	
≥30.9	0.35 (18)	0.39 (30)	0.89 (0.50 to 1.60)	
Physical activity, metabolic equivalent units, h/wk				.77
<2.5	0.40 (17)	0.44 (28)	0.88 (0.48 to 1.62)	
2.5 to <11.3	0.37 (18)	0.44 (32)	0.85 (0.47 to 1.51)	
≥11.3	0.41 (19)	0.44 (31)	0.92 (0.52 to 1.63)	
Percentage of energy from fat§				.05
<28.7	– (23)	– (26)	1.33 (0.76 to 2.33)	
28.7 to <35.1	– (14)	– (35)	0.60 (0.32 to 1.12)	
≥35.1	– (14)	– (36)	0.58 (0.31 to1.08)	
Fat intake, g/day§				.06
<54.5	– (21)	– (28)	1.13 (0.64 to 1.98)	
54.5 to <70.4	– (18)	– (32)	0.84 (0.47 to 1.50)	
≥70.4	– (12)	– (37)	0.49 (0.25 to 0.93)	
Vegetable and fruit intake, servings/day‖				.79
<2.6	0.29 (15)	0.45 (35)	0.63 (0.35 to 1.16)	
2.6 to <4.1	0.46 (24)	0.43 (34)	1.05 (0.62 to 1.77)	
≥4.1	0.32 (17)	0.43 (34)	0.75 (0.42 to 1.34)	
Grain intake, servings/day‖				.13
<3.4	0.46 (24)	0.45 (35)	1.03 (0.61 to 1.73)	
3.4 to <5.3	0.36 (19)	0.34 (27)	1.01 (0.56 to 1.82)	
≥5.3	0.25 (13)	0.51 (41)	0.48 (0.26 to 0.89)	

* Hazard ratio from a proportional hazards model stratified by age and hormone replacement therapy randomization arm (active hormones, placebo, or nonparticipant, separately for women with or without a uterus). $P_{interaction}$ of a score test of interaction between random group assignment and variable of interest.

† Among mothers, sisters, or daughters, and, for breast cancer, also grandmothers.

‡ Self-report of pills or shots.

§ From an analysis of 4-day food records from ovarian cancer patients. These "case-only" analyses do not yield incidence rate estimates.

‖ From food-frequency questionnaire; classification based on tertiles for entire cohort.

On the topic of multiple testing, we note that a hazard ratio trend test as extreme as $P = .01$ remains statistically significant at the 5% level when the Bonferroni correction for the five "diet-related" cancer sites is performed. Hence, the observed trend in ovarian cancer hazard ratio cannot easily be attributed to chance. The hazard ratio of 0.60 (95% CI = 0.38 to 0.96, $P = .03$) for the latter half of the intervention period is of particular interest in the context of this statistically significant hazard ratio trend, whereas the overall hazard ratio of 0.83 (95% CI = 0.60 to 1.14) can be viewed as diluted by little or no intervention effect during the early intervention years, as anticipated in trial design.

Table 4. Women's Health Initiative Dietary Modification trial intervention versus comparison group hazard ratios (HRs) and 95% confidence intervals (CIs) for total invasive cancer by baseline characteristics and dietary factors

Variable	Incidence per 1000 person-years (No. of cases)		HR (95% CI)*	$P_{interaction}$
	Intervention (N = 1687)	Comparison (N = 2661)		
Age at screening, y				.61
50–59	7.95 (483)	8.41 (769)	0.94 (0.84 to 1.06)	
60–69	11.41 (821)	12.16 (1312)	0.93 (0.86 to 1.02)	
70–79	15.27 (383)	15.36 (580)	0.99 (0.87 to 1.13)	
Race/ethnicity				.93
White	11.33 (1461)	11.82 (2300)	0.96 (0.89 to 1.02)	
Black	7.63 (130)	8.45 (21)	0.90 (0.72 to 1.12)	
Hispanic	7.29 (42)	7.69 (65)	0.96 (0.65 to 1.42)	
Asian/Pacific Islander	8.02 (27)	8.90 (47)	1.01 (0.62 to 1.64)	
American Indian	5.55 (4)	8.97 (8)	0.81 (0.23 to 2.82)	
Other	11.75 (23)	10.14 (31)	1.24 (0.72 to 2.13)	
Personal history of cancer†				.07
Yes	11.99 (80)	15.82 (160)	0.74 (0.57 to 0.98)	
No	10.64 (1591)	10.97 (2462)	0.97 (0.91 to 1.03)	
History of oral contraceptive use				.79
Yes	9.51 (680)	9.90 (1059)	0.96 (0.87 to 1.06)	
No	11.67 (1007)	12.31 (1602)	0.94 (0.87 to 1.02)	
Diabetes‡				.72
Yes	12.63 (84)	13.60 (138)	0.92 (0.70 to 1.21)	
No	13.60 (1603)	11.12 (2523)	0.95 (0.89 to 1.01)	
Body mass index, kg/m^2				.65
<24.9	9.56 (396)	10.38 (647)	0.91 (0.81 to 1.04)	
24.9–<28.2	10.61 (596)	10.95 (931)	0.97 (0.88 to 1.08)	
28.2–<32.5	11.50 (412)	12.17 (660)	0.94 (0.83 to 1.06)	
≥32.5	11.59 (275)	11.99 (413)	0.98 (0.84 to1.14)	
Physical activity, metabolic equivalent units, h/wk				.82
<1.5	11.14 (377)	11.67 (598)	0.94 (0.83 to 1.07)	
1.5 to <6.3	10.33 (365)	11.15 (578)	0.91 (0.80 to 1.04)	
6.3 to <14.8	11.13 (375)	11.85 (620)	0.94 (0.83 to 1.07)	
≥14.8	10.82 (376)	10.71 (551)	1.01 (0.89 to 1.16)	
Percentage of energy from fat§				.51
<33.8	11.08 (455)	10.57 (618)	1.06 (0.94 to 1.20)	
33.8 to <36.9	10.06 (391)	11.45 (684)	0.86 (0.76 to 0.98)	
36.9 to <40.8	10.36 (402)	10.92 (652)	0.94 (0.83 to 1.07)	
≥40.8	11.24 (442)	11.89 (696)	0.94 (0.84 to 1.06)	
Fat intake, g/day§				.59
<52.3	10.72 (417)	11.20 (659)	0.95 (0.84 to 1.08)	
52.3 to <68.9	11.10 (440)	11.16 (661)	0.99 (0.88 to 1.12)	
68.9 to <91.2	10.45 (415)	11.52 (679)	0.90 (0.80 to 1.02)	
≥91.2	10.48 (408)	10.96 (651)	0.95 (0.84 to 1.08)	
Vegetable and fruit intake, servings/day§				.65
<2.3	10.96 (428)	11.28 (663)	0.97 (0.86 to 1.09)	
2.3 to <3.3	10.19 (401)	10.68 (633)	0.94 (0.83 to 1.07)	
3.3 to <4.6	10.31 (408)	11.03 (654)	0.94 (0.83 to 1.06)	
≥4.6	11.29 (443)	11.85 (700)	0.96 (0.85 to 1.08)	
Grain intake, servings/day§				.29
<3.0	10.89 (421)	11.12 (652)	0.98 (0.87 to 1.11)	
3.0 to <4.3	11.08 (445)	11.27 (661)	0.98 (0.87 to 1.11)	
4.3 to <5.9	11.81 (449)	11.81 (698)	0.95 (0.84 to 1.07)	
≥5.9	9.42 (365)	10.64 (639)	0.88 (0.78 to 1.01)	

* Hazard ratio from a proportional hazards model stratified by age and hormone replacement therapy randomization arm (active hormones, placebo, or nonparticipant, separately for women with or without a uterus). $P_{interaction}$ of a score test of interaction between random group assignment and variable of interest.

† Exclusive of nonmelanoma skin cancer.

‡ Self-report of pills or shots.

§ From food-frequency questionnaire; classification based on quartiles for entire cohort.

Table 5. Comparison of incidence rates for "other" cancer sites between intervention and comparison groups in the Women's Health Initiative (WHI) Dietary Modification trial

Site grouping/site	Incidence per 1000 person-years (No. of cases)		*P**	HR (95% CI)*
	Intervention	Comparison		
Gynecologic	0.18 (28)	0.19 (45)	.90	0.94 (0.59 to 1.51)
Cervix	0.03 (4)	0.05 (13)	.50	0.46 (0.15 to 1.42)
Genital organs	0.07 (11)	0.06 (14)	.66	1.20 (0.54 to 2.63)
Uterus, NOS†	0.08 (13)	0.08 (18)	.79	1.08 (0.53 to 2.21)
Renal/urinary	0.42 (66)	0.51 (121)	.43	0.82 (0.61 to 1.10)
Kidney	0.20 (31)	0.25 (60)	.92	0.78 (0.50 to 1.20)
Bladder	0.21 (33)	0.23 (55)	.55	0.90 (0.58 to 1.38)
Urinary organs (NOS)	0.01 (2)	0.03 (7)	.10	0.43 (0.09 to 2.06)
Digestive	0.61 (97)	0.61 (144)	.95	1.01 (0.78 to 1.31)
Oropharynx/esophagus‡	0.13 (21)	0.14 (34)	.47	0.93 (0.54 to 1.60)
Stomach	0.09 (14)	0.08 (19)	.67	1.10 (0.55 to 2.19)
Biliary tract	0.11 (17)	0.05 (13)	.20	1.96 (0.95 to 4.03)
Pancreas	0.20 (32)	0.27 (65)	.44	0.75 (0.49 to 1.15)
Liver	0.07 (11)	0.03 (7)	.31	2.30 (0.89 to 5.93)
Other§	0.03 (4)	0.03 (6)	.83	0.99 (0.28 to 3.50)
Respiratory	0.86 (136)	0.94 (223)	.73	0.92 (0.74 to 1.13)
Lung	0.86 (136)	0.93 (221)	.80	0.92 (0.75 to 1.14)
Other‖	0 (0)	0.01 (3)	–	–
Brain/nervous system	0.15 (24)	0.13 (30)	.89	1.20 (0.70 to 2.05)
Brain	0.15 (24)	0.13 (30)	.89	1.20 (0.70 to 2.05)
Nervous system	0 (0)	0 (0)	–	–
Bones/connective tissue	0.23 (37)	0.27 (64)	.78	0.86 (0.57 to 1.29)
Bones, joints, cartilage	0.02 (3)	0.02 (5)	.65	0.86 (0.21 to 3.60)
Connective/soft tissue	0.04 (7)	0.05 (12)	.94	0.87 (0.34 to 2.22)
Multiple myeloma	0.17 (27)	0.20 (47)	.82	0.86 (0.53 to 1.38)
Blood/lymphatic	0.74 (116)	0.80 (189)	.40	0.92 (0.73 to 1.16)
Hodgkin disease	0.01 (1)	0.03 (8)	.05	0.19 (0.02 to 1.51)
Non-Hodgkin lymphoma	0.47 (74)	0.48 (114)	.62	0.97 (0.72 to 1.30)
Leukemia	0.25 (40)	0.27 (64)	.95	0.94 (0.63 to 1.40)
Lymph nodes	0.02 (3)	0.01 (3)	.88	1.49 (0.30 to 7.40)
Endocrine	0.19 (30)	0.20 (47)	.98	0.96 (0.61 to 1.52)
Thyroid	0.16 (26)	0.16 (39)	.78	1.00 (0.61 to 1.65)
Other¶	0.03 (4)	0.03 (8)	.55	0.75 (0.23 to 2.49)
Other sites	1.23 (194)	1.22 (290)	.77	1.01 (0.84 to 1.21)
Melanoma of skin	0.51 (81)	0.49 (117)	.88	1.04 (0.78 to 1.38)
Other/unknown site#	0.72 (113)	0.73 (173)	.61	0.99 (0.78 to 1.25)

* *P* from weighted log-rank test (two-sided) stratified by age (5-year categories) and randomization status in the WHI hormone therapy trial (active hormones, placebo, or nonparticipant, separately among women with or without a uterus). Weights increase linearly from zero at random assignment to a maximum of 1.0 at 10 years. HR = hazard ratio; CI = confidence interval, from proportional hazards model stratified by age (5-year categories) and randomization status in the WHI hormone therapy trial.

† NOS = not otherwise specified.

‡ Includes mouth, tongue, palate, salivary glands, sinus, larynx, and esophagus.

§ Includes appendix and anus.

‖ Includes intrathoracic and "respiratory system, other."

¶ Includes adrenal, parotid, and "endocrine glands, related structures."

Includes cancers listed only on death reports.

Perhaps the strongest data in favor of an intervention effect on ovarian cancer risk derive from analyses of hazard ratios in relation to baseline percentage of energy from fat. We have previously noted (3) that women whose baseline dietary fat intakes is high achieve a larger reduction in the percentage of energy from fat than do women with lower baseline dietary fat intakes, if assigned to the dietary intervention group. The women in the highest tertile of fat intake at baseline correspondingly had smaller ovarian cancer hazard ratios than women in the lowest tertile (Table 3).

The suggestion (P = .10) of a modestly reduced total invasive cancer hazard ratio among intervention group women (HR = 0.95, 95% CI = 0.89 to 1.01) could be of some practical importance. Also, the total cancer hazard ratio interaction analyses (Table 4) suggest a lower risk of invasive cancer in the intervention versus comparison group among women having a personal history of cancer before trial enrollment. The 1-year FFQ difference in percentage of energy from fat between randomization groups was slightly larger (P = .04) for women with a personal history of cancer (11.45%) than for women without such a history (10.72%), so it is possible that differences in adherence to the dietary intervention could contribute to this suggested interaction.

The results seen in Table 5 for Hodgkin disease (P = .05, HR = 0.19), biliary tract cancer (P = .20, HR = 1.96), and liver cancer (P = .31, HR = 2.30) can readily be attributed to chance. They arise in the context of approximately 25 comparisons, each based on a small number of disease events. Also, the limited observational literature for biliary tract and liver cancer mostly (8,20), but not entirely (21), tend to suggest a positive association with dietary fat.

In summary, the DM trial indicates that a low-fat eating pattern may reduce ovarian cancer risk (P = .03), although this finding needs to be interpreted in the context of comparisons for five cancer sites. The DM trial also suggests (P = .10) a possible reduction in total invasive cancer. Ongoing nonintervention follow-up of trial participants may provide additional valuable assessment of the effects of a low-fat dietary pattern on these and other cancer incidence rates.

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Clinical Trials Registration—ClinicalTrials.gov identifier: NCT00000611. Decisions concerning study design, data collection and analysis, interpretation of the results, the preparation of the manuscript, or the decision to submit the manuscript for publication resided with committees comprising WHI investigators that included National Heart, Lung, and Blood Institute representatives. An external Data and Safety Monitoring Committee met twice yearly throughout the study intervention period, and recommended changes, as appropriate to the sponsor. This study proceeded to its planned termination date.

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A full listing of WHI investigators can be found at the following Web site: http://www.whi.org.

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