Research Article

Cancer Epidemiology, Biomarkers & Prevention

Low-Fat Diet and Skin Cancer Risk: The Women's Health Initiative Randomized Controlled Dietary Modification Trial

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Abstract

Background: Large cohort studies have reported no relationship between dietary fat and nonmelanoma skin cancer (NMSC), although a low-fat diet intervention reduced NMSC risk in a small clinical trial. In animal studies, skin tumor development has been reduced by low-fat diet. We evaluated the effect of a low-fat dietary pattern on NMSC and melanoma in the Women's Health Initiative Dietary Modification trial.

Methods: Postmenopausal women aged 50 to 79 years ($n = 48,835$) were randomly assigned to the low-fat dietary pattern intervention ($n = 19,541$) or comparison group ($n = 29,294$). The intervention goals included decreasing fat intake to 20% or less of calories, increasing vegetable and fruit intake, and increasing grain intake. Self-reported incident NMSC ($n = 4,907$) and physician-adjudicated incident melanoma ($n = 279$) were ascertained every 6 months.

Results: Over 8.1 years of follow-up, the low-fat diet intervention did not affect overall incidence of NMSC [HR 0.98; 95% confidence interval (CI), 0.92–1.04] or melanoma (HR, 1.04; 95% CI, 0.82–1.32). In subgroup analyses of melanoma risk, baseline fat intake interacted significantly with group assignment ($P_{interaction} = 0.006$). Among women with higher baseline fat intake, the dietary intervention significantly increased risk (HR, 1.48; 95% CI, 1.06–2.07), whereas, among women with lower baseline fat intake, the intervention tended to reduce melanoma risk (HR, 0.72; 95% CI, 0.50–1.02).

Conclusions: In this large randomized trial, a low-fat dietary pattern did not affect overall incidence of NMSC or melanoma.

Impact: A low-fat diet does not reduce incidence of NMSC, but an interaction between baseline fat intake and dietary intervention on melanoma risk warrants further investigation. *Cancer Epidemiol Biomarkers Prev; 22(9); 1509–19. ©2013 AACR.*

Introduction

Skin cancer is the most common malignancy in the United States, affecting more than 2 million individuals in 2006, which is double the incidence reported in 1994 (1, 2). The American Cancer Society estimated that Americans would develop 3.5 million new cases of nonmelanoma skin cancer (i.e., basal cell and squamous cell carcinomas) and 76,250 new cases of melanoma in 2012 (1, 3). Sun exposure is the main established risk factor for skin cancer; however, only part of the variation in skin cancer incidence is explained by variables related to sun exposure (4–7). Despite public health campaigns emphasizing sunscreen use and sun avoidance, incidences of nonmelanoma skin cancer (NMSC) and melanoma continue to rise, especially among women (8–10). Consequently, there is a great need to identify other modifiable risk factors for skin cancer and new approaches for skin cancer prevention.

Clinical studies of dietary fat and NMSC are inconsistent (11–18). One large prospective cohort found no relationship between dietary fat intake and NMSC risk in women, while another noted lower NMSC risk with higher dietary fat intake in men (16, 18). On the other hand, a 2-year randomized trial of subjects with a history of NMSC reported that a low-fat diet intervention reduced NMSCs in the last 8 months of the study, but not in the first 16 months (11, 20). The clinical data on dietary fat and melanoma are also inconsistent (19–24).

There is a biologic rationale for an association between fat intake and risk of skin cancer. Laboratory studies have shown that a high-fat diet contributes to oxidative stress and DNA damage (25), increasing inflammatory

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Table 1. Baseline characteristics of participants[a]

	Intervention ($n = 19,541$) *N* (%)	Comparison ($n = 29,294$) *N* (%)
Age, y		
50–59	7,206 (36.9)	10,792 (36.8)
60–69	9,083 (46.5)	13,632 (46.5)
70–79	3,252 (16.6)	4,870 (16.6)
Race/ethnicity		
White	15,871 (81.2)	23,891 (81.6)
Black	2,135 (10.9)	3,127 (10.7)
Hispanic	751 (3.8)	1,094 (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		
Less than high school diploma or GED	4,267 (21.8)	6,468 (22.1)
Some school after high school diploma	7,712 (39.5)	11,597 (39.6)
College degree or higher	7,446 (38.1)	11,044 (37.7)
Body mass index (kg/m^2)		
<25	5,072 (26.0)	7,587 (25.9)
25–<30	6,944 (35.5)	10,452 (35.7)
≥30	7,442 (38.1)	11,125 (38.0)
Smoking status		
Never	9,918 (50.8)	15,029 (51.3)
Past	8,121 (41.6)	11,979 (40.9)
Current	1,273 (6.5)	1,977 (6.7)
NSAID use		
Yes	6,316 (32.3)	9,796 (33.4)
No	13,224 (67.7)	19,498 (66.6)
Total vitamin D intake, IU[b]		
<200 IU	7,763 (39.7)	11,892 (40.6)
200 to <400 IU	3,986 (20.4)	5,787 (19.8)
400 to <600 IU	4,454 (22.8)	6,602 (22.5)
≥600 IU	3,226 (16.5)	4,892 (16.7)
Total energy intake, kcal		
<1,296	4,820 (24.7)	7,327 (25.0)
1,296 to <1,677	4,924 (25.2)	7,226 (24.7)
1,677 to <2,150	4,879 (25.0)	7,267 (24.8)
≥2,150	4,807 (24.6)	7,353 (25.1)
Percent energy from total fat,%		
<33.8	4,892 (25.0)	7,109 (24.3)
33.8 to <36.9	4,885 (25.0)	7,536 (25.7)
36.9 to <40.8	4,752 (24.3)	7,285 (24.9)
≥40.8	4,901 (25.1)	7,243 (24.7)
Total fat intake, grams		
<52.4	4,828 (24.7)	7,322 (25.0)
52.4 to <69.0	4,897 (25.1)	7,265 (24.8)
69.0 to <91.2	4,893 (25.0)	7,243 (24.7)
≥91.2	4,812 (24.6)	7,343 (25.1)
Total vegetable and fruit servings per day		
<2.3	5,013 (25.7)	7,500 (25.6)
2.3 to <3.3	4,696 (24.0)	7,090 (24.2)
3.3 to <4.6	4,755 (24.3)	7,104 (24.3)
≥4.6	4,966 (25.4)	7,479 (25.5)

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Table 1. Baseline characteristics of participants[a] (Cont'd)

	Intervention ($n = 19,541$) *N* (%)	Comparison ($n = 29,294$) *N* (%)
Total grain servings per day		
<3.0	4,789 (24.5)	7,250 (24.7)
3.0 to <4.3	5,096 (26.1)	7,407 (25.3)
4.3 to <5.9	4,727 (24.2)	7,029 (24.0)
≥5.9	4,818 (24.7)	7,487 (25.6)
Regional solar radiation, langleys[c]		
300–325	5,661 (29.0)	8,512 (29.1)
350	3,801 (19.5)	5,701 (19.5)
375–380	2,292 (11.7)	3,435 (11.7)
400–430	3,398 (17.4)	5,088 (17.4)
475–500	4,381 (22.4)	6,548 (22.4)
Total outdoor walking energy expenditure, METs/wk		
0	6,714 (34.4)	9,817 (33.5)
≤3.5	3,791 (19.4)	5,790 (19.8)
3.6–7.0	3,341 (17.1)	5,114 (17.5)
>7.0	3,661 (18.7)	5,532 (18.9)
History of cancer[d]		
Yes	853 (4.4)	1,286 (4.4)
No	18,688 (95.6)	28,008 (95.6)
History of melanoma		
Yes	122 (0.6)	170 (0.6)
No	19,419 (99.4)	29,124 (99.4)
History of nonmelanoma skin cancer		
Yes	1,264 (6.5)	1,996 (6.8)
No	18,277 (93.5)	27,298 (93.2)
Hormone therapy use		
Never used	8,072 (41.3)	12,102 (41.3)
Past user	2,813 (14.4)	4,181 (14.3)
Current user	8,639 (44.2)	12,979 (44.3)
Hormone therapy intervention assignment		
Not randomly assigned	16,359 (83.7)	24,426 (83.4)
Active	1,587 (8.1)	2,496 (8.5)
Placebo	1,595 (8.2)	2,372 (8.1)
Calcium/vitamin D intervention assignment		
Not randomly assigned	9,896 (50.6)	13,729 (46.9)
Active	4,767 (24.4)	7,827 (26.7)
Placebo	4,878 (25.0)	7,738 (26.4)

[a]Percentages may not total 100% because of missing data.
[b]From diet and supplements.
[c]Based on the mean annual amount of sunlight reaching the clinic site as measured by the U.S. Weather Bureau; 1 langley = 1 g-cal/cm^2.
[d]History of cancer (cancers diagnosed more than 10 years before enrollment) is defined as any cancer except nonmelanoma skin cancer.
GED, general equivalency diploma; MET, metabolic equivalent tasks.

cytokines in the skin while decreasing cell apoptosis (26). One study found a nearly linear relationship between increasing lipid level and development of actinic tumors in mice, noting both shorter time to tumor formation and greater number of tumors (27). Another study noted that low-fat diet was associated with slower melanoma tumor growth (28).

The Women's Health Initiative (WHI) Dietary Modification (DM) Trial of 48,835 postmenopausal women, designed to evaluate whether a low-fat dietary pattern intervention would decrease the incidence of breast and colorectal cancers (primary outcomes) and/or coronary heart disease (secondary outcome; ref. 29–32), provides an opportunity to investigate whether a low-fat dietary

pattern reduces the risk of NMSC or melanoma within a large randomized controlled trial.

Materials and Methods

Study population

The WHI DM Trial (NCT00000611) design has been described previously, as have eligibility criteria and recruitment methods (29, 33, 34). Briefly, postmenopausal women, aged 50 to 79 years, were recruited at 40 Clinical Centers throughout the United States between 1993 and 1998. Major exclusions included previous history of breast, colorectal, or any cancer other than nonmelanoma skin cancer in the past 10 years; predicted survival of less than 3 years; type I diabetes mellitus; and other conditions that posed adherence and retention concerns (e.g., alcoholism, dementia; ref. 33). Participants had to have a baseline fat intake 32% or more of total energy, as estimated by the WHI Food Frequency Questionnaire (FFQ).

Study design

Eligible women ($n = 48{,}835$) were randomly assigned by permuted block algorithm to either the dietary intervention (40%, $n = 19{,}541$) or the comparison group (60%, $n = 29{,}294$). The dietary goals for the intervention group included decreasing total fat intake to 20% or less of energy and consuming 5 or more servings per day of vegetables and fruits and 6 or more servings per day of grains. The women received an individualized dietary plan with a daily fat gram goal based on their expected energy intake (29). The intervention did not include weight loss or total energy reduction goals. Women in the intervention group participated in nutritionist-facilitated small group sessions (18 sessions during year 1 and quarterly sessions each year thereafter). Women assigned to the comparison group received a copy of *Nutrition and Your Health: Dietary Guidelines for Americans* but were not asked to change their diet (30, 35). The trial design for comparison–intervention difference in percentage of energy from total fat was 13% at year 1 and 11.75% at year 6. Among all participants, the actual comparison–intervention difference at year 1 and year 6 was 10.7% and 8.1%, respectively (30).

Demographic information, medical history, and other characteristics were obtained by questionnaire or physical measurement at study entry (baseline). This analysis included all women enrolled in the DM Trial, except participants with missing data for body mass index (BMI) at baseline. All procedures and protocols were approved by the Institutional Review Boards at each participating institution and all participants provided written informed consent.

Follow-up and data collection

On average, women in the DM Trial were followed for 8.1 years (SD, 1.6 years). As of March 2005, the percentage of women still actively participating in the trial was similar between the 2 groups, with 17,674 women in the dietary intervention group (90.4%) and 26,677 in the comparison group (91.1%; ref. 30). Clinical measures (such as weight) and self-reported measures (such as physical activity) of the participants were collected during annual clinic visits (29).

The WHI FFQ was used to assess dietary intake in both groups. All participants completed the FFQ at baseline (before randomization) and year 1. After year 1, a rotating sample of 33% of participants was surveyed each year, such that each participant completed a FFQ every 3 years. A detailed description of the FFQ validation has been published (36). The response rate to the FFQ was 100% at baseline and approximately 81% in subsequent years (32). The nutrient database was derived from the University of Minnesota Nutrition Coordinating Center nutrient database (NDSR, Minneapolis, Minnesota; ref. 36).

Outcome ascertainment

Participants completed questionnaires every 6 months to report medical outcomes, including NMSC and melanoma (37). Melanoma cases were confirmed by adjudication of pathology reports, and coded as invasive or *in situ* following the ICD-O-2 coding scheme (38). NMSC cases were not adjudicated.

Statistical analysis

Baseline descriptive characteristics, potential skin cancer risk factors, and dietary intake were compared in the intervention and comparison groups. Differences in each category were evaluated using χ^2 tests for categorical variables and t tests for continuous variables.

In *post hoc* analyses, incidence of NMSC and melanoma were compared between the groups using HRs with 95% confidence intervals (CI) and Wald statistic P values from Cox proportional hazards models. The proportionality assumption was confirmed by running a proportional hazards model that modeled each outcome as a function of the interaction between the low-fat dietary pattern effect and the log survival time. Modeling analyses used time-to-event methods according to the intention-to-treat principle. Kaplan–Meier estimates were provided to describe event rates over time. As in prior analyses of the DM Trial (30), sensitivity analyses were conducted by censoring intervention participants who missed an annual clinic visit, failed to participate in 9 or more of the 18 first year group sessions, or failed to participate in 2 or more of the 4 group sessions in subsequent years; or comparison participants who missed an annual clinic visit. With these criteria, the adherence rates in the intervention group were 57% at year 3, 31% at year 6, and 19% at year 9, whereas the adherence rates in the comparison group were 87%, 75%, and 65% (30). All proportional hazards models were stratified by age groups at recruitment (50–54, 55–59, 60–69, and 70–79) and randomized treatment assignment in the other WHI clinical trials (34), that is, the Hormone Therapy Trials of combined estrogen and progestin (39) or estrogen only (40) and the Calcium/Vitamin D Trial (41).

Table 2. Number of nonmelanoma skin cancer and melanoma events by overall trial and sensitivity analysis

	Number of cases (annualized %)			
Overall trial	**Intervention (n = 19,541)**	**Comparison (n = 29,294)**	**HR (95% CI)[a]**	**P[b]**
NMSC	1,923 (1.28)	2,984 (1.32)	0.98 (0.92–1.04)	0.44
Melanoma	114 (0.07)	165 (0.07)	1.04 (0.82–1.32)	0.78
	Number of cases (annualized %)			
Sensitivity analysis[c]	**Intervention**	**Comparison**	**HR (95% CI)[a]**	**P[b]**
NMSC	977 (1.27)	2,470 (1.34)	0.99 (0.92–1.07)	0.76
Melanoma	54 (0.07)	136 (0.07)	1.04 (0.75–1.43)	0.83

[a]All models were adjusted for age, assignment in the Hormone Therapy trial, and assignment in the Calcium/Vitamin D trial.
[b]2-sided (from Cox proportional hazards model).
[c]Sensitivity analysis censored women who did not comply with trial requirements (e.g., participants from the intervention group who missed an annual clinic visit, failed to participate in ≥9 of the 18 first year group sessions, or failed to participate in ≥2 of the 4 group sessions in subsequent years; or comparison participants who missed an annual clinic visit).

To assess whether the effect of low-fat dietary pattern on NMSC or melanoma risk varied according to baseline risk factors for both types of skin cancer, Cox proportional hazards models were extended to include the variable of interest and interaction with group assignment. HRs for intervention versus comparison within each subgroup are presented along with the $P_{interaction}$. Twelve predefined subgroup analyses were conducted for NMSC and melanoma to assess possible statistical interactions between a low-fat dietary pattern and the following known or potential skin cancer risk factors at baseline: (i) age, (ii) BMI, (iii) regional solar radiation, (iv) history of NMSC, (v) smoking status, (vi) use of nonsteroidal anti-inflammatory drug (NSAID), (vii) vitamin D intake, (viii) total energy intake, (ix) percentage of energy from total fat intake, (x) total fat intake, (xi) vegetable and fruit servings, and (xii) grain servings. Cut-off points for age, BMI, and regional solar radiation were previously defined in the WHI clinical trials. For NMSC, baseline dietary intake was evaluated by quartiles determined by the natural distribution of participants' intake at baseline. For melanoma, as there were fewer cases, baseline dietary intake is presented by 2 methods: the intake groups for energy and fat are divided into an top and bottom half determined by the mean intake of the cohort, whereas the intake groups for vegetable and fruit servings and grain servings are presented by the upper quartile versus the lower three quartiles to reflect current intake recommendations for cancer prevention (42, 43). All statistical analyses were completed using SAS 9.2 (SAS Institute Inc). All statistical tests were two-sided.

Results

Baseline characteristics of participants

Table 1 shows baseline characteristics of participants in the dietary intervention and comparison groups. Participants had an average age of 62.3 years (SD, 6.9 years) and an average BMI of 29.1 kg/m^2 (SD, 5.9 kg/m^2). The demographics, health behaviors, skin cancer risk factors [i.e., sun exposure (measured via regional solar radiation and total outdoor walking) and history of NMSC and melanoma), and medical history were comparable between the randomization groups.

Nonmelanoma skin cancer

Incidence of self-reported NMSC was similar between randomization groups over an average follow-up of 8.1 years, with 1,923 NMSC cases in the dietary intervention group and 2,984 cases in the comparison group (annualized percentage of 1.28% vs. 1.32%; HR, 0.98; 95% CI, 0.92–1.04; Table 2; Fig. 1). Even when

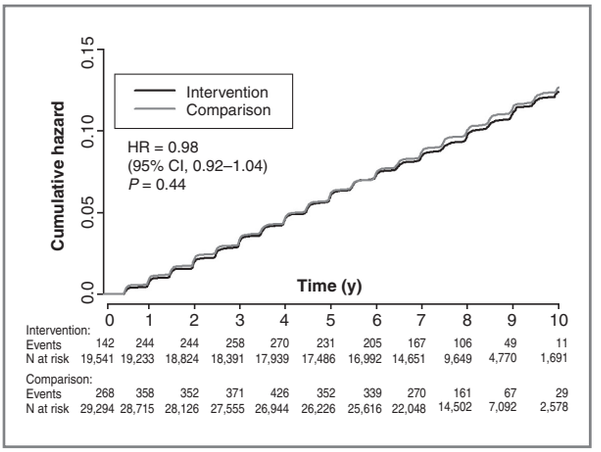

Figure 1. Kaplan–Meier estimate of cumulative hazards for nonmelanoma skin cancer events (n = 4,907). Cox proportional hazards, Wald statistic $P_{interaction}$.

Table 3. Estimated effect of dietary modification on risk of melanoma, according to selected baseline characteristics

	Intervention		Comparison			
Subgroup	**Events**	**Ann%**	**Events**	**Ann%**	**HR (95% CI)[a]**	***P***
Overall	*114*	*0.07*	*165*	*0.07*	*1.04 (0.82–1.32)*	
Age, y						0.25
50–59	41	0.07	62	0.07	0.99 (0.67–1.47)	
60–69	54	0.08	78	0.07	1.04 (0.73–1.46)	
70–79	19	0.08	25	0.07	1.15 (0.63–2.09)	
BMI, kg/m^2						0.13
<25	28	0.07	46	0.07	0.91 (0.57–1.46)	
25–<30	36	0.06	66	0.08	0.83 (0.55–1.24)	
≥30	50	0.08	52	0.06	1.43 (0.97–2.11)	
Langley exposure[b]						0.64
≤375	451	1.05	85	0.07	1.03 (0.73–1.43)	
>375	449	1.11	80	0.07	1.05 (0.74–1.47)	
History of NMSC						0.31
Yes	22	0.22	26	0.16	1.37 (0.77–2.41)	
No	92	0.06	139	0.06	0.99 (0.76–1.29)	
Smoking						0.59
Never	62	0.08	84	0.07	1.12 (0.80–1.55)	
Past	46	0.07	73	0.08	0.93 (0.64–1.34)	
Current	6	0.06	6	0.04	1.57 (0.51–4.87)	
NSAID use						0.42
Yes	44	0.09	58	0.07	0.96 (0.71–1.30)	
No	70	0.07	107	0.07	1.18 (0.80–1.75)	
Total vitamin D intake, IU[c]						0.89
<400	64	0.07	97	0.07	0.99 (0.72–1.36)	
≥400	49	0.08	67	0.07	1.10 (0.76–1.58)	
Total energy intake, kcal						0.66
<1677	67	0.09	91	0.08	1.11 (0.81–1.52)	
≥1677	47	0.06	73	0.06	0.97 (0.67–1.39)	
Percent energy from total fat,%						0.006
<36.9	45	0.06	94	0.08	0.72 (0.50–1.02)	
≥36.9	69	0.09	70	0.06	1.48 (1.06–2.07)	
Total fat intake, grams						0.18
<69.0	60	0.08	95	0.08	0.95 (0.69–1.32)	
≥69.0	54	0.07	69	0.06	1.17 (0.82–1.67)	
Vegetable and fruit servings/day						0.037
<4.6	89	0.08	106	0.06	1.26 (0.95–1.67)	
≥4.6	25	0.06	58	0.10	0.65 (0.41–1.03)	
Grain servings/day						0.43
<5.9	96	0.08	124	0.07	1.15 (0.88–1.50)	
≥5.9	18	0.05	40	0.07	0.69 (0.40–1.21)	

[a]All models were adjusted for age, assignment in the Hormone Therapy trial, and assignment in the Calcium/Vitamin D trial.
[b]Based on the mean annual amount of sunlight reaching the clinic site as measured by the US Weather Bureau; the 1 langley = 1 g = cal/cm^2.
[c]From diet and supplements.

participants with a history of NMSC were excluded, NMSC incidence did not differ between the groups (HR, 0.97; 95% CI, 0.91–1.04), nor did NMSC outcomes differ by group assignment within any of the predefined subgroups [i.e., age, BMI, regional solar radiation (langleys), history of NMSC, smoking, NSAID use, vitamin D intake, total energy or fat intake, or vegetable and fruit servings; Table 4].

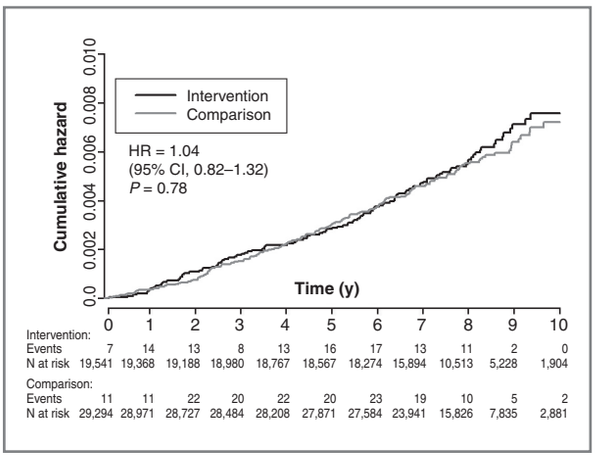

Figure 2. Kaplan–Meier estimate of cumulative hazards for melanoma events ($n = 279$). Cox proportional hazards, Wald statistic $P_{interaction}$.

Melanoma

Incidence of physician-adjudicated melanoma was similar between randomization groups, with 114 melanoma cases in the dietary intervention group and 165 cases in the comparison group (annualized percentage of 0.07% vs. 0.07%; HR, 1.04; 95% CI, 0.82–1.32; Table 2; Fig. 2). Melanoma incidence was similar between the groups even when participants with a history of melanoma were excluded (HR, 1.04; 95% CI, 0.82–1.32); however, in subgroup analysis, there was a significant differential effect of low-fat dietary intervention on risk of melanoma by baseline fat intake ($P_{interaction} = 0.006$). Specifically, women with higher baseline fat intake (≥36.9% of total energy, or the upper half of baseline intake as determined by the mean of the participants) had a significantly higher melanoma risk (HR, 1.48; 95% CI, 1.06–2.07), whereas women with lower baseline fat intake (<36.9% of total energy) trended toward lower melanoma risk (HR, 0.72; 95% CI, 0.50–1.02) when assigned to dietary intervention versus comparison (Table 3, Fig. 3). A significant differential effect of the low-fat dietary intervention on melanoma risk was also found by baseline vegetable and fruit intake ($P_{interaction} = 0.037$), with women in the lower 3 quartiles of vegetable and fruit servings per day at baseline (≤ 4.6) trending toward higher risk of melanoma (HR, 1.26; 95% CI, 0.95–1.67), whereas women in the upper quartile tended to have lower melanoma risk (HR, 0.65; 95% CI, 0.41–1.03) when assigned to dietary intervention versus comparison. Dietary intervention did not affect melanoma within any other subgroups.

Sensitivity analysis

In analyses in which participants who did not fully comply with the trial requirements were censored (e.g., participants from the intervention group who missed an annual clinic visit, failed to participate in ≥ 9 of the 18 first year group sessions, or failed to participate in ≥ 2 of the 4 group sessions in subsequent years; or comparison participants who missed an annual clinic visit; ref. 30), incidences of NMSC and melanoma were similar in the intervention and comparison groups (NMSC: HR, 0.99; 95% CI, 0.92–1.07; melanoma: HR 1.04; 95% CI, 0.75–1.43; Table 2). Limiting the primary analysis to Caucasian women showed similar results, with no significant difference in incidence of NMSC or melanoma. A time-dependent analysis of weight loss did not alter the relationship between diet and skin cancer risk (data not shown).

Discussion

The WHI Dietary Modification Trial is the largest randomized controlled trial to evaluate whether a low-fat dietary pattern, with decreased fat intake and increased vegetable, fruit, and grain intake, reduces cancer risk in postmenopausal women. A low-fat dietary pattern did not affect the overall incidence of nonmelanoma skin cancer or melanoma over an average 8.1-years of follow-up.

Although the comparison–intervention difference in percent of energy from total fat was lower than anticipated, the intervention group maintained a significant long-term difference in the percentage of energy from total fat versus the comparison group (−8.1%, $P < 0.001$; refs. 30, 44), as well as vegetable and fruit intake (1.1 servings per day, $P < 0.001$) and grain intake (0.4 servings per day, $P < 0.001$; refs. 30, 37). Even though these differences were small, this dietary intervention was shown to reduce breast cancer risk significantly among participants in the upper quartile of dietary fat at baseline, thus suggesting that biologically meaningful changes in diet were achieved in the WHI DM Trial (30). Notably, the small but significant decrease in polyunsaturated fat in the WHI intervention versus comparison group (−1.5% at year 6, $P < 0.001$; ref. 32) was not associated with risk of skin cancers, consistent with several studies of NMSC (11, 12, 16, 18) and melanoma (22–24).

Our overall null results are consistent with several observational studies that found no association between fat intake (16, 17) or vegetable and fruit intake (15, 17, 18) and risk of NMSCs (i.e., basal cell and/or squamous cell carcinomas). A 4-year prospective study of 73,366 women without history of skin cancer in the Nurses' Health Study found no overall association between dietary fat intake and incidence of basal cell carcinoma (16), while an 8-year prospective study of 43,217 men without history of skin cancer in the Health Professionals Follow-up Study found that higher percentage of energy from total fat was associated with lower risk of basal cell carcinoma (18). An 11-year prospective cohort within a randomized trial of beta-carotene and daily sunblock also found no overall association between dietary fat intake and incidences of basal cell and squamous cell carcinoma (12).

In a previous 2-year trial (11) of low-fat diet, the average number of NMSCs among 101 participants with a history of skin cancer was only lower in the last 8 months of the intervention, suggesting that greater follow-up might be required to determine the effect of diet on skin cancer. However, in our 8-year trial we saw no effect of dietary

Table 4. Estimated effect of dietary modification on risk of nonmelanoma skin cancer (NMSC), according to selected baseline characteristics

	Intervention		Comparison			
Subgroup	**Events**	**Ann%**	**Events**	**Ann%**	**HR (95% CI)[a]**	***P***
Overall	*1,923*	*1.28*	*2,984*	*1.32*	*0.98 (0.92–1.04)*	
Age, y						0.17
50–59	505	0.86	824	0.93	0.93 (0.83–1.04)	
60–69	953	1.39	1,472	1.44	0.98 (0.91–1.07)	
70–79	465	2.00	688	1.97	1.03 (0.91–1.15)	
BMI, kg/m^2						0.26
<25	641	1.65	932	1.59	1.06 (0.96–1.17)	
25 to <30	687	1.28	1,145	1.42	0.92 (0.84–1.01)	
≥30	589	1.03	896	1.05	0.97 (0.88–1.08)	
Langley exposure[b]						0.74
≤375	908	1.23	1,382	1.24	0.98 (0.90–1.07)	
>375	1,015	1.33	1,602	1.40	0.98 (0.90–1.06)	
History of NMSC						0.64
Yes	471	5.96	754	5.99	1.01 (0.90–1.13)	
No	1,452	1.02	2,230	1.05	0.97 (0.91–1.04)	
Smoking						0.93
Never	956	1.25	1,517	1.30	0.97 (0.89–1.05)	
Past	842	1.35	1,287	1.40	0.98 (0.90–1.07)	
Current	103	1.07	156	1.03	1.02 (0.80–1.31)	
NSAID use						0.14
Yes	634	1.31	1063	1.42	0.92 (0.84–1.02)	
No	1,289	1.27	1,921	1.28	1.01 (0.94–1.08)	
Total vitamin D intake, IU[c]						0.43
<400	1,053	1.15	1,643	1.19	0.97 (0.90–1.05)	
≥400	863	1.48	1,330	1.53	0.99 (0.91–1.08)	
Total energy intake, kcal						0.62
<1,296	397	1.07	672	1.20	0.92 (0.81–1.04)	
1,296 to <1677	525	1.39	737	1.32	1.06 (0.95–1.19)	
1677 to <2150	512	1.37	824	1.47	0.93 (0.83–1.04)	
≥2150	482	1.30	740	1.31	1.01 (0.90–1.13)	
Percent energy from total fat,%						0.20
<33.8	512	1.36	803	1.47	0.95 (0.85–1.06)	
33.8–<36.9	489	1.30	783	1.35	0.96 (0.86–1.07)	
36.9–<40.8	488	1.34	753	1.34	1.01 (0.90–1.13)	
≥40.8	427	1.14	634	1.14	1.01 (0.90–1.15)	
Total fat intake, grams						0.44
<52.4	412	1.11	696	1.24	0.92 (0.81–1.04)	
52.4–<69.0	504	1.34	762	1.36	0.99 (0.89–1.11)	
69.0–<91.2	516	1.37	784	1.41	0.98 (0.88–1.10)	
≥91.2	484	1.31	731	1.29	1.02 (0.91–1.14)	
Vegetable and fruit servings/day						0.67
<2.3	391	1.01	621	1.07	0.94 (0.83–1.07)	
2.3–<3.3	455	1.25	727	1.33	0.95 (0.85–1.07)	
3.3–<4.6	507	1.39	738	1.35	1.04 (0.93–1.16)	
≥4.6	563	1.49	887	1.55	0.98 (0.88–1.09)	
Grain servings/day						0.95
<3.0	435	1.19	690	1.25	0.99 (0.87–1.11)	
3.0–<4.3	515	1.31	797	1.40	0.96 (0.86–1.07)	
4.3–<5.9	526	1.45	766	1.42	1.00 (0.90–1.12)	
≥5.9	440	1.18	720	1.24	0.97 (0.86–1.09)	

[a]All models were adjusted for age, assignment in the Hormone Therapy trial, and assignment in the Calcium/Vitamin D trial.
[b]Based on the mean annual amount of sunlight reaching the clinic site as measured by the US Weather Bureau; 1 langley = 1 g-cal/cm^2.
[c]From diet and supplements.

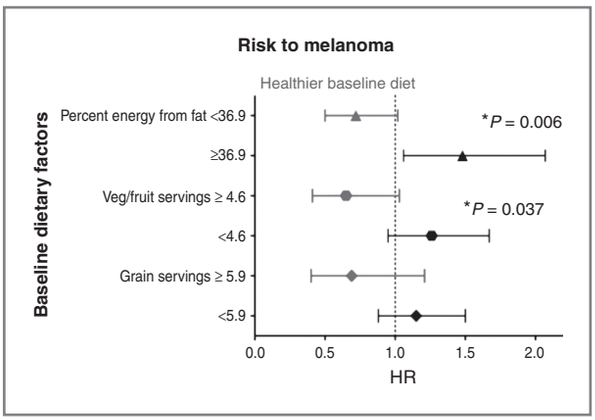

Figure 3. Effect of dietary modification on risk of melanoma, according to baseline dietary factors targeted by intervention ($n = 279$). Cox proportional hazards, Wald statistic $P_{interaction}$. *Models were adjusted for age, assignment in the Hormone Therapy trial, and assignment in the Calcium/Vitamin D trial.

intervention on NMSC among participants with a history of skin cancer. Notably, the trial by Black and colleagues (11) achieved a greater decrease in percentage of energy from total fat than in the DM Trial (30).

Our results are the first to evaluate melanoma risk within a randomized trial of low-fat diet. One prospective cohort (19) and several case–control studies (21–24) showed no association between total fat intake (19, 21–24) or vegetable and fruit intake (24) and melanoma. Other studies found lower risk of melanoma with higher fat intake (20) and vegetable and fruit intake (21). In subgroup analysis, we found a significant, differential effect of low-fat diet on melanoma risk depending on baseline fat intake of participants, and also vegetable and fruit intake. Women with higher baseline fat intake (≥36.9% of total energy) assigned to dietary intervention had a higher risk of melanoma, whereas women with lower baseline fat intake (32 to 36.9%) trended toward lower melanoma risk. A similar differential effect was seen among participants in the intervention group by baseline vegetable and fruit intake. Thus, perhaps women with unhealthier baseline diets (e.g., high fat intake and low vegetable and fruit intake at baseline) assigned to dietary intervention became more health-conscious during the trial, and underwent skin examination leading to increased diagnosis of melanoma. Other studies have shown that healthy habits, such as physical activity and healthy diet, may be associated with cancer screening (45, 46). In contrast, participants in the intervention group with healthier baseline diets (e.g., moderate-fat intake and greater vegetable and fruit intake at baseline) may have achieved an even lower fat diet than their counterparts in the intervention group, leading to a trend toward lower melanoma risk. Further investigations on the effect of greater dietary modification than that achieved in the WHI DM Trial on risk of melanoma may be merited. Notably, these results should be interpreted with caution given the multiple subgroups tested.

The strengths of this study include the randomized dietary intervention, the large diverse study population, and the long follow-up time. This analysis is the first to assess melanoma risk within a randomized controlled trial of low-fat diet. This study has several limitations. The primary limitation is that the intervention group did not achieve the comparison–intervention goal, and the percentage of participants who adhered to the trial requirements decreased as the trial progressed. However, a sensitivity analysis that was restricted to those who complied did not show an effect of low-fat dietary pattern on risk of skin cancers. Furthermore, these adherent participants achieved a comparison–intervention difference that was closer to the trial goal (at year 1, 12.1%, and at year 6, 11.1%; ref. 30). Like many previous studies of diet and skin cancer, recorded dietary intake was dependent on self-report. Greater underreporting has been associated with higher BMI (47), but FFQ self-reported diet has been shown to correlate with nutritional biomarkers and chronic disease measures in some studies, but not all (30, 48). However, the validity of FFQ may be less critical given the randomized treatment assignment and large sample size. In addition, as the WHI DM Trial was designed to examine the effect of a low-fat dietary pattern on breast and colorectal cancer as well as cardiovascular disease, *post hoc* analyses of melanoma risk may lack statistical power to detect differences. Finally, this study was dependent upon self-report of NMSCs with no indication of type (e.g., basal cell or squamous cell carcinoma), but others have found self-report of skin cancer to be reliable (49, 50).

In conclusion, our results do not support a role for reducing dietary fat to prevent skin cancer in postmenopausal women. However, further investigations of lower fat diets in women who are consuming a baseline moderate-fat diet, or of larger dietary change, are relevant areas for future research in melanoma prevention.

Disclosure of Potential Conflicts of Interest

J.Y. Tang is a consultant/advisory board member of Genentech. The other authors disclosed no potential conflicts of interest.

Authors' Contributions

Conception and design: M. Stefanick, J.Y. Tang
Development of methodology: M. Stefanick, J.Y. Tang
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Stefanick, L. Van Horn, J.Y. Tang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.S. Gamba, M. Stefanick, J. Larson, E. Linos, J.R. Marshall, J.Y. Tang
Writing, review, and/or revision of the manuscript: C.S. Gamba, M. Stefanick, J. Shikany, J. Larson, E. Linos, S.T. Sims, J.R. Marshall, L. Van Horn, N. Zeitouni, J.Y. Tang
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.S. Gamba, J. Larson, J.Y. Tang
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Low-Fat Diet and Skin Cancer Risk: The Women's Health Initiative Randomized Controlled Dietary Modification Trial

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