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Cost-Effectiveness Analysis of a Low-Fat Diet in the Prevention of Breast and Ovarian Cancer

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ABSTRACT

Background Results of the Women's Health Initiative Randomized Controlled Dietary Modification Trial (WHI-DM) suggest that a low-fat diet may be associated with beneficial health outcomes for specific groups of women.

Objective The objective is to assess how cost-effective the WHI-DM would be if implemented as a public health intervention and under the sponsorship of private health insurers and Medicare. Breast and ovarian cancers are the health outcomes of interest.

Participants Two groups of WHI-DM participants form the target population for this analysis: participants consum-

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ing >36.8% of energy from fat at baseline, and participants at high risk for breast cancer with 32% or more of energy from fat at baseline.

Methods This study uses Markov cohort modeling, following societal and health care payer perspectives, with Monte Carlo simulations and one-way sensitivity analyses. WHI-DM records, nationally representative prices, and published estimates of medical care costs were the sources of cost information. Simulations were performed for hypothetical cohorts of women aged 50, 55, 60, 65, or 70 years at the beginning of the intervention. Effectiveness was estimated by quality-adjusted life years (QALYs) and the main outcome measure was the incremental cost-effectiveness ratio (ICER).

Results Following the societal perspective, the ICERs for the 50-year old cohort are \$13,773/QALY (95% confidence interval \$7,482 to \$20,916) for women consuming >36.8% of energy from fat at baseline and \$10,544/QALY (\$2,096 to \$23,673) for women at high risk for breast cancer. The comparable ICER from a private health care payer perspective is \$66,059/QALY (\$30,155 to \$121,087) and from a Medicare perspective, it is \$15,051/QALY (\$6,565 to \$25,105).

Conclusions The WHI-DM is a cost-effective strategy for the prevention of breast and ovarian cancers in the target population, from both societal and Medicare perspectives. Private health care payers have a relative short timeframe to realize a return on investment, since after age 65 years the financial benefits associated with the prevention program would accrue to Medicare. For this reason, the intervention is not cost-effective from a private health care payer perspective.

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The Women's Health Initiative Randomized Controlled Dietary Modification Trial (WHI-DM) assessed the effects of a low-fat dietary pattern on the prevention of cancer. The total enrollment was 48,835 postmenopausal women, 50 to 79 years of age, without prior cancer and with diets featuring $\geq 32\%$ of energy from fat as assessed by a food frequency questionnaire (FFQ) during screening (1). The trial was conducted at 40 US clinical centers from 1993 to 2005. The intervention was successful in promoting dietary change, as the fat intake was significantly lower in the intervention than in the comparison group during follow-up. The difference between the intervention and the comparison groups in change from baseline for percentage of energy from fat varied from 10.7% at Year 1 to 8.1% at Year 6. Women whose baseline dietary fat intake was high achieved a larger reduction in the percentage of energy from fat than did women with lower baseline dietary fat intakes, if assigned to the dietary intervention group (2). There was evidence of reductions in the incidence of breast cancer in subgroup analyses and in ovarian cancer after 4 years from randomization. The strongest data in favor of an intervention effect on cancer risk derive from analyses of hazard ratios in relation to baseline fat intake. Women with higher fat intakes were more likely to achieve reductions in the incidence of breast and ovarian cancers (2,3).

The effective behavior modification program and the beneficial health outcomes lead to interest in replicating the program as a public health intervention, so that women who did not participate in the WHI-DM study, but that present a similar profile, can receive the benefits of a low-fat diet. To provide additional information for such considerations, a cost-effectiveness analysis was used to evaluate the outcomes and costs of the WHI-DM program (4). If the program is associated with relative low costs compared to outcomes, this finding provides support for public health officials and other decision makers to invest in a similar intervention for a wider group of the population. These findings are particularly relevant in the context of the Patient Protection and Affordable Care Act enacted on March 23, 2010, which provides emphasis to competition, cost reductions, comparative effectiveness, and preventive services. Our analysis addresses segments of the population where the effectiveness of the intervention is clearly established. Specifically, two sets form the target population: women with >36.8% of energy intake from fat at baseline and women at high risk for breast cancer with $\geq 32\%$ of energy from fat at baseline. Notice that every participant in the WHI-DM trial met or exceeded the 32% threshold, as this was one criterion for participation in the trial. The study uses new estimates of the hazard ratios associated with the intervention and it follows the recommendations of the US Public Health Service Panel on Cost Effectiveness in Health and Medicine (5).

METHODS

Cost-Effectiveness Analysis

The result of the cost-effectiveness analysis is summarized by the incremental cost-effectiveness ratio (ICER). The ICER is calculated as the difference between the total cost in the intervention group and the total cost in the comparison group, divided by the difference between the health outcomes in the intervention group and the health outcomes in the comparison group. It indicates the additional cost of obtaining a unit of health effect from the low-fat dietary intervention compared with the regular diet. Health outcomes are estimated by quality-adjusted life years (QALYs), which measures the time spent in a series of quality-weighted health states (disease-free, cancer, death), where the quality weights reflect the desirability of living in the state (6,7). The quality weights (also called utility ratios) represent the preferences for the health states under consideration which, by convention, vary from zero (death) to one (perfect health). With this convention, the resulting QALY is measured in units of years lived in full health. The advantage of the QALY as a measure of health output is that it can simultaneously capture gains from reduced cancer morbidity (quality gains) and reduced mortality (quantity gains), and it incorporates the value or preferences people place on different outcomes. It captures all important health dimensions of the effect of the intervention. Following standard recommendations (8), future costs and outcomes were discounted to present-day values using a real rate of 3.0%.

Perspectives

A cost-effectiveness study can be undertaken from different perspectives, according to which agent is making the decision to implement a given health intervention. A societal perspective considers everyone affected by the intervention and counts all significant health outcomes and costs from it, regardless of who experiences them (4). This perspective is appropriate for decisions on the efficient allocation of societal resources for health care (9) and it is the standard perspective for public health decisions (4). A second alternative is to use a health care payer perspective, which only considers the costs to private insurers—if the participant is younger than age 65 years-and to Medicare—if the participant is aged 65 years or older. For private insurers, this analysis indicates if there is a business case to offer an intervention similar to WHI-DM, based on a financial return on investment in the form of avoided cancer treatment costs and cost-sharing strategies within a reasonable period (10). For Medicare, this analysis assesses the potential effect on its budget and the desirability of a similar program offered to its participants.

The private payer perspective is implemented by including in the analysis only the participants who were between 50 and 55 years old at the beginning of the intervention. The costs and outcomes of the WHI-DM program are calculated up to an age of 65 years, since after this age the treatment costs are borne by Medicare. Private payers need to recover their investment before the participant turns 65 years old since, beyond this age, Medicare would benefit financially from the prevention program.

The Medicare perspective is implemented by including in the analysis only the participants who started the WHI program at age 65 years or older. The costs and outcomes of the intervention are calculated from that age through the expected end of life. Medicare does not pay for preventive interventions for people younger than age 65 years and it does not have authority to pay for services offered to non-Medicare beneficiaries.

A common practice among analysts conducting cost-effectiveness research is to compare the ICERs obtained in their research with conventional thresholds that reflect an acceptable willingness-to-pay level by society or relevant decision makers. Following the most common convention for the society perspective, interventions with ICER <\$50,000 are considered very cost-effective, whereas interventions with ICER >\$100,000 are considered ineffective (11,12). These figures are controversial, since plausible lower and upper bounds for a cost-effectiveness decision rule that are substantially higher that these values have been proposed (13,14). Nevertheless, the conventional thresholds are used below as a general guide for the interpretation of the results.

The scope of the health-care payer perspective is more constrained. For public payers, such as Medicare, and non-profit private payers, the intervention should be, ideally, cost reducing, given the savings associated with the lower cancer incidence. However, given its public health mandate, Medicare should not focus exclusively on cost saving when making coverage decisions (15). In this case, a relatively low ICER would indicate that the intervention is an efficient use of Medicare resources. For instance, England's National Health Service uses a £20,000/QALY threshold, approximately \$30,000/QALY (16).

Private, profit-oriented health care payers have, strictly speaking, a weaker interest on QALYs as a relevant outcome. Still, if the QALY-based ICER is reasonably low, the private payer could have an incentive to offer the program, if profit were generated by charging a fee for participation, co-payments, deductibles or other cost-sharing strategies. For instance, Ackermann and colleagues (10) relied on a low, private-payer perspective ICER to consider possible cost-sharing schemes that would provide private payers with a financial return on their investment.

Markov Model

A Markov cohort model (17) was designed using TreeAge Pro 2009 software (release 1.02, 2009, TreeAge Software, Inc, Williamstown, MA) to follow hypothetical cohorts of participants through four health states: cancer-free, breast cancer, ovarian cancer, and death. All research subjects began the Markov process free of cancer and they were followed until death or age 100 years in annual cycles. Five cohorts are included in the study, defined by the age when they started the WHI-DM program: 50, 55, 60, 65, and 70 years. The private health care payer perspective included only the cohorts aged 50 and 55 years, and the participants were followed until death or age 65 vears. To generate estimates for the standard deviations of the ICERs, 10,000 Monte Carlo probabilistic simulations were performed in each case, where the model parameters were simultaneously sampled over their probability distributions.

The Markov model used in this study is similar to those used in cancer prevention studies (18-23). Three sets of age-dependent transition probabilities are included. The first set is the probability of evolving from disease-free to breast or ovarian cancer. Women with breast cancer could subsequently develop ovarian cancer, with the same conditional probability as those who were well (18). Cancer risks are distinct between the intervention and comparison groups, as the low-fat diet is associated with lower cancer incidence. Breast cancer was modeled as a tunnel state of 10 years' duration, after which no woman dies of breast cancer, but she remains at risk of developing ovarian cancer and dying from other causes (21). The second set is the probability of dying from breast or ovarian cancer during the cycle. The third set is the probability of dying from unrelated causes. The second and third components are identical between the groups, since the intervention did not have an influence on cancer mortality (2) and since low-fat diets, similar to that used in the WHI-DM, do not have undesirable side effects (24,25).

The age adjusted, target-specific cancer incidence rates for years 1993 to 2006 from the National Cancer Institute SEER program (SEER*Stat, version 6.5.2, 2009, National Cancer Institute, Bethesda, MD) were converted into annual conditional probabilities (26). For the highfat group of WHI-DM participants, defined as the median FFQ baseline assessment (>36.8% energy from fat), the probability of breast cancer was increased by 10% (2). Women at high risk for breast cancer have three times the age-specific probability of breast cancer incidence as the general population, based on hazard ratio analyses, including BRCA1 and/or BRCA2 genetic mutations, one first-degree relative with breast cancer diagnosed at an early age, high breast tissue density, biopsy-confirmed atypical hyperplasia, high bone density (postmenopausal), high-dose radiation to chest (27). In addition, as all WHI-DM participants did, they feature diets with \geq 32% of energy from fat. This strategy was implemented by multiplying by three the age-specific probability of breast cancer incidence provided in the SEER database. For mortality, the crude probability of death, using expected survival from the SEER program was used. The 5-year risks were converted to annual conditional probabilities of death by assuming constant instantaneous death rates per year within each 5-year period. For noncancer death, breast and ovarian cancers were removed as causes of death from the US cohort-based life tables (National Vital Statistics Reports deaths from each cause; www.cdc.gov).

Table 1 provides the cumulative hazard ratios for breast cancer associated with the WHI-DM intervention and the results of unweighted significance tests for the target population. The hazard ratio is a measure of how often the onset of cancer happened in the intervention group compared to how often it happened in the comparison group, over time. A hazard ratio <1 indicates that cancer incidence was lower in the intervention group. In the estimation of these ratios, the data were stratified by age groups and by randomization in the hormone therapy trial. The inverse of the participant's estimated adherence probability was used as a weighting factor. The 8-year time frame used in these calculations reflects the median follow-up used in the WHI-DM trial. Two sets of hazard ratios are presented. The first uses the time from randomization to event—onset of cancer, death, or loss to follow-up—to contrast intervention and comparison groups. The second set uses time from the first group meeting to event for the intervention group, while still using time from randomization for the comparison group. The two groups are compared in the same length of time, up to 8 years, but they have distinct starting points. The main motivation of this strategy is that, although the waiting period between randomization and the beginning of the intervention varied for each individual participant, the median waiting period was relatively long: 84 days. For 25% of the participants, the wait was over 4 months.
 Table 1.
 Cumulative hazard ratios (HRs) for invasive breast cancer associated with the Women's Health Initiative Randomized Controlled Dietary

 Modification Trial (WHI-DM) intervention

	н	Rs from Rand	lomization Date		HRs from Intervention Start				
	All WHI-DM Participants		WHI-DM Participants with High Fat Intake ^a		All WHI-DM Pa	irticipants	WHI-DM Participants with High Fat Intake ^a		
Year	HR±SD ^b	P value	HR±SD	P value	HR±SD	P value	HR±SD	P value	
1	0.948±0.183	0.78	0.843±0.162	0.69	1.066±0.194	0.726	0.955±0.264	0.707	
2	0.842 ± 0.096	0.13	0.694 ± 0.097	0.07	0.958 ± 0.105	0.698	0.762±0.124	0.303	
3	0.826 ± 0.072	0.03	$0.685 {\pm} 0.078$	0.02	0.862 ± 0.074	0.082	0.744 ± 0.091	0.127	
4	0.904 ± 0.067	0.18	0.806 ± 0.080	0.28	0.944 ± 0.069	0.429	0.914 ± 0.098	0.706	
5	0.941 ± 0.062	0.36	0.804 ± 0.072	0.23	0.887 ± 0.058	0.066	0.766 ± 0.072	0.099	
6	0.782 ± 0.047	< 0.001	0.672 ± 0.054	< 0.001	0.620 ± 0.037	< 0.001	$0.543 {\pm} 0.046$	< 0.001	
7	0.909 ± 0.049	0.08	0.782 ± 0.058	0.07	0.580 ± 0.032	< 0.001	0.511 ± 0.040	< 0.001	
8	$0.915 {\pm} 0.048$	0.09	$0.770 {\pm} 0.055$	0.04	$0.778 {\pm} 0.041$	< 0.001	0.671 ± 0.050	< 0.001	
^a WHI-DM participants with high fat intakes (ie, $>$ 36.8% of energy from fat at baseline), as assessed by food frequency questionnaire. ^b SD = standard deviation									

Using time from the first group meeting may more closely reflect the influence of a low-fat diet in the incidence of breast cancer, since participants were not expected to change their diets during the waiting period. An important result in this sensitivity analysis is that the 0.778 hazard ratio for all WHI-DM participants, cumulative to the 8th year from the beginning of the intervention reported in Table 1, is statistically significant at a 5% level, indicating that, from this perspective, a low-fat diet significantly reduces cancer incidence for women whose diets have >32% of energy from fat at baseline. Table 1 also reports that, cumulative to the 8th year, the intervention is associated with significant reductions in breast cancer for participants with >36.8% of energy from fat at baseline, irrespective of which set of hazard ratios is used.

For ovarian cancer, the small number of cases implies that any yearly estimates would be unreliable. The published hazard ratio was used (0.60; 95% confidence interval 0.38-0.96), following the assumption that the intervention has no significant affect on ovarian cancer during the first 4 years (3).

The source of cancer-specific utility ratios—quality weights—was Anderson and colleagues (18). These ratios were multiplied by the age-adjusted utilities for healthy women provided by Stout and colleagues (23). This procedure follows the recommendations of Gold and colleagues (5), and it addresses the observation that a life saved would not be lived in perfect health, and therefore, the utility value of 1.0 should not be used for it. The ranges for the utility ratios between ages 50 and 85 years 0.780 to 0.590 for healthy women, 0.601 to 0.454 for women with breast cancer, and 0.507 to 0.384 for women with ovarian cancer.

Intervention Costs

The cost-effectiveness analysis performed by this study is based on a comprehensive estimate of the monetary and nonmonetary costs associated with the behavioral modification program and dietary regimen. The main objective of these calculations is to estimate the cost of the program if applied as a new health intervention, not to recover the historic costs associated with the WHI-DM research. For this purpose, the costs of research activities, such as collecting, processing, and interpreting clinical data, including electrocardiograms and mammograms, are not considered. On the same lines, costs that are common to both intervention and comparison groups are not included, such as printing, completing, and processing the FFQ. The costs are calculated using the level of resources used in the dietary modification intervention and newly collected market prices for these resources, including staff wages. All costs are adjusted by the consumer price index to reflect 2008 prices, whereas health care costs are adjusted by the medical care component of the index.

The main feature of the dietary modification program was a series of orientation and support meetings, guided by behavior change principles (28,29). These meetings imply two sets of costs: opportunity costs for the participants—as they could engage in other activities instead of attending these meetings—and direct expenditures for staff, equipment, supplies, materials, and facilities.

The opportunity costs to participants were estimated by multiplying the average number of hours attended by the 2008 median hourly earnings of wage and salary women paid hourly rates (30). The WHI-DM intervention protocol specified 18 group intervention sessions during the first year, followed by four group meetings in each of the follow-up years and one individual dietary counseling session in the first year. Group and individual make-up sessions were also available. The group meetings lasted between 90 and 120 minutes, whereas the individual counseling session was 1 hour long. The average attendance per participant was 13.6 sessions in the first year, 15.5 sessions during the follow-up years, 0.91 individual counseling sessions and 6.7 make-up sessions. The opportunity costs for women younger and older than age 65 years were estimated separately, since the hourly earning for the younger women (\$13) was significantly higher than for the older women (\$10.53).

	Opportunity Costs ^a ±SD ^b		Monetary	Costs±SD	Average Diet Costs±SD		
Year	Age<65 y	Age≥65 y	Staff	Other ^c	Comparison	Intervention	
1	540.96±15.53	445.86±12.80	452.27±110.91	340.34±83.46	1,649.09±5.76	1,719.31±6.76	
2	110.55 ± 1.00	94.81 ± 0.85	76.94 ± 18.87	61.45±15.07			
3	108.43 ± 0.88	92.99 ± 0.75	76.94±18.87	61.43 ± 15.07	1,635.40±6.86	1,713.03±8.36	
4	103.21 ± 0.98	88.02 ± 0.84	76.94 ± 18.87	61.43 ± 15.07			
5	99.07±1.13	84.56 ± 0.96	76.94 ± 18.87	69.68±17.09			
6	95.50±1.18	80.82 ± 0.99	76.94±18.87	61.43 ± 15.07	1,628.32±6.26	1,654.97±7.30	
7	85.73±1.20	68.91 ± 0.96	76.94±18.87	62.89±15.42			
8	69.11 ± 1.07	$51.87 {\pm} 0.80$	76.94±18.87	67.05±16.44			
^a Based on	time commitment to attend	meetings and perform self-r	nonitoring activities.				

Direct expenditures for staff were estimated based on the time commitment collected from WHI-DM records, adjusted by the average group size (12 participants) or, if appropriate, by the average clinical center size (456 participants). The majority of the intervention activities were provided by staff with moderate level of responsibility and expertise (equivalent to dietary technicians with at least a 2-year associate's degree). Staff with high level of responsibility and expertise (equivalent to dieticians with at least a bachelor's degree) assisted with the screening, led the dietary modification intervention at each clinical center and facilitated two intervention group sessions during the first year. Staff at the low level primarily assisted in the screening process. The hourly wage rates for the staff-\$15.50/hour for staff at low level, \$19.35/hour for staff at the moderate level, \$24.75 for staff at the high level-were based on nationally representative figures (31-33). Estimates of the training costs for staff were also included. WHI-DM guidelines provided the requirements for facilities, equipment, supplies, and printed materials. Prices for these items were collected at retail and on-line sources. Information about the dietary patterns of the intervention and comparison groups was gathered from the WHI FFQ, and analyzed by the Nutrition Assessment Shared Resource of the Fred Hutchinson Cancer Research Center. The Nutrition Assessment Shared Resource estimated the consumption level of specific food items, and multiplied this consumption information with food prices, using standard US Department of Agriculture food codes. The nationally representative Center for Nutrition Policy Promotion Prices Database provided by the US Department of Agriculture (34) was used. For the purposes of this analysis, intervention participants were considered to have remained with the lowfat diet until they develop cancer.

Women in the intervention group were asked to selfmonitor their intake of fat, fruits, vegetables, and grains (35-37). This is part of the research protocol, as self monitoring is a well-documented aid in changing behaviors and maintaining the changes. A variety of tools was used during the program: Fat Counter, Fat Scan, Keeping Track of Goals, Quick Scan, and Picture Tracker. The publication of these tools carries a monetary cost, and their use involves a time commitment by the participants. Based on WHI-DM records, on average each participant spent 80.2 hours using these tools during the course of the intervention.

A lower incidence of cancer implies that treatment costs will be avoided (7). Since the WHI-DM program did not collect health care costs for cancer treatment, cost estimates from the literature were used. In the societal and private payer perspectives, the net costs associated with breast and ovarian cancers provided by Fireman and colleagues (38) were used. In the Medicare perspective, the net costs provided by Yabroff and colleagues (39) were used. The cancer care costs were specified by the state of treatment: initial care (first 12 months following cancer onset), continuing care per year, terminal care (last 12 months of life).

Table 2 provides yearly estimates of the intervention costs per participant, in 2008 prices. The societal perspective includes all costs. The health care payer perspectives exclude opportunity and diet costs. Health care costs with cancer treatment are not included in Table 2, but they are available in the sources indicated above (38,39).

Table 2 indicates that the WHI-DM implies a substantial time commitment by participants to attend the meetings and perform self-monitoring activities. Using a 3% yearly discount rate, the present value of the opportunity cost over the 8 years is \$1,110.04 for participants younger than age 65 years and \$923.17 for participants aged 65 years and older. The present value of direct costs per participant over the 8 years is \$1,619.25. Table 2 indicates that a low-fat diet costs slightly more than a regular diet, a difference ranging from 4.1% at the end of the first year of intervention to 1.6% in the sixth year.

RESULTS

Societal Perspective

Table 3 presents the results of the cost-effectiveness analysis according to the societal perspective. For women at high risk for breast cancer, the hazard ratios for "all WHI-DM participants" from Table 1 were used. Strictly speaking, this strategy is justified only if the hazard

Table 3. Cost-effectiveness of the Women's Health Initiative Randomized Controlled Dietary Modification Trial following societal perspective								
	Hazard Ratios from Randomization Date					Hazard Ratios from Intervention Start		
Start age	Group	Total cost	Effectiveness	ICER ^a (95% CI ^b)	Total cost	Effectiveness	ICER (95% CI)	
Participants with high fat intake at baseline (>36.8% of energy from fat)								
50 y	Comparison	\$44,100	15.841 QALYs ^c		\$44,100	15.841 QALYs		
-	Intervention	\$45,264	15.926 QALYs	\$13,773/QALY (7,482-20,916)	\$45,211	15.927 QALYs	\$12,944/QALY (6,170-22,026)	
55 y	Comparison	\$40,692	13.847 QALYs		\$40,692	13.847 QALYs		
	Intervention	\$41,907	13.921 QALYs	\$16,560/QALY (8,988-25,233)	\$41,852	13.922 QALYs	\$15,551/QALY (7,155-26,581)	
60 y	Comparison	\$36,720	12.368 QALYs		\$36,720	12.368 QALYs		
	Intervention	\$38,004	12.431 QALYs	\$20,349/QALY (11,282-31,824)	\$37,983	12.431 QALYs	\$20,009/QALY (9,356-35,818)	
65 y	Comparison	\$32,143	10.695 QALYs		\$32,143	10.695 QALYs		
	Intervention	\$33,465	10.746 QALYs	\$26,146/QALY (14,552-41,293)	\$33,463	10.745 QALYs	\$26,312/QALY (12,429-48,764)	
70 y	Comparison	\$27,267	8.911 QALYs		\$27,267	8.911 QALYs		
	Intervention	\$28,806	8.949 QALYs	\$41,085/QALY (24,689-63,929)	\$28,827	8.947 QALYs	\$42,842/QALY (21,834-80,347)	
Participants at high risk for breast cancer with \geq 32% of energy from fat								
50 y	Comparison	\$58,730	15.395 QALYs		\$58,730	15.395 QALYs		
	Intervention	\$60,259	15.474 QALYs	\$19,199/QALY (7,988-38,446)	\$59,733	15.490 QALYs	\$10,544/QALY (2,096-23,673)	
55 y	Comparison	\$54,620	13.455 QALYs		\$54,620	13.455 QALYs		
	Intervention	\$56,116	13.525 QALYs	\$21,394/QALY (8,037-46,886)	\$55,611	13.538 QALYs	\$14,885/QALY (1,725-28,767)	
60 y	Comparison	\$49,601	12.023 QALYs		\$49,601	12.023 QALYs		
	Intervention	\$51,078	12.084 QALYs	\$24,059/QALY (7,315-59,582)	\$50,701	12.093 QALYs	\$15,604/QALY (2,324-42,915)	
65 y	Comparison	\$43,398	10.413 QALYs		\$43,398	10.413 QALYs		
	Intervention	\$44,836	10.463 QALYs	\$28,442/QALY (8,296-78,367)	\$44,555	10.469 QALYs	\$20,461/QALY (3,394-59,610)	
70 y	Comparison	\$36,655	8.695 QALYs		\$36,655	8.695 QALYs		
	Intervention	\$38,235	8.734 QALYs	\$40,769/QALY (12,333-125,315)	\$38,071	8.736 QALYs	\$34,450/QALY (8,861-115,219)	
^a ICER=	incremental cost-	effectiveness	ratio.					
^b CI=confidence interval.								
^c OALY=quality-adjusted life years								

notice from the intermention start are used but th

ratios from the intervention start are used, but the results from both sets of hazard ratios are presented.

The results indicate that the WHI-DM is a very costeffective intervention in the prevention of breast and ovarian cancers for women with high fat intakes and for women at high breast cancer risk. In most cases in Table 3, even the upper bound limit of the 95% confidence interval is lower than the conventional, \$50,000 to \$100,000/QALY thresholds. Likewise, most point estimates in Table 3 are below the \$27,000 median ICER for breast cancer interventions as reported in a systematic overview of cost-utility analyses in oncology (40). The ICERs for women at high risk for breast cancer are less reliable than those for women with high fat intakes, given their wider confidence intervals. The ICERs are lower for the younger participants, but the intervention remains cost effective for all age groups.

Given the high costs of cancer treatment, the reduced cancer incidence in the intervention group is associated with significant cost savings. For instance, for the highfat group, starting the intervention at age 50 years and using hazard ratios from randomization, the estimated present value of the expected health care costs for a participant in the intervention group is \$8,188, whereas for a participant in the control group the estimated costs are \$10,661. These medical care savings (\$2,473) are higher than the direct costs of the intervention (\$1,619.25; as indicated in Table 2).

For women with high fat intakes (>36.8% of energy

from fat), there are no important differences between the ICERS according to which set of hazard ratios is used. For women at high risk for breast cancer, the ICERs that use hazard ratios from intervention are substantially lower. This distinction reflects the results presented in Table 1, where the eighth year cumulative hazard ratio from randomization for all WHI-DM participants was not statistically significant, whereas the hazard ratio from intervention was significant.

Health Care Payer Perspectives

Table 4 shows the cost-effectiveness from the health-care payer perspectives. For participants who started the intervention at ages 50 and 55 years, these estimates follow a private health care payer perspective. For participants who started the intervention at age 65 and 70 years, Medicare is the health care payer.

The results shown in Table 4 indicate that private providers would have no interest in offering the WHI-DM program to women younger than age 65 years. The costs of the intervention outweigh the health care savings and the high ICER suggests that cost sharing between care payers and patients would not be feasible (10). The ICERs are very unreliable, as indicated by the wide confidence intervals. On the other hand, it is very cost-effective for Medicare to offer the intervention to its participants, especially for the younger cohort.
 Table 4.
 Cost-effectiveness following health-care payer perspective, based on results of the Women's Health Initiative Randomized Controlled

 Dietary Modification Trial

			Hazard Ratios	from Randomization Date	Hazard Ratios from Intervention Start		
Start age	Group	Total cost	Effectiveness	ICER ^a (95% CI ^b)	Total cost	Effectiveness	ICER (95% CI)
Participants with high fat intake at baseline (>36.8% of energy from fat)							
50 y	Comparison	\$3,271	9.271 QALYs ^c		\$3,271	9.271 QALYs	
-	Intervention	\$4,168	9.284 QALYs	\$66,059/QALY (30,155-121,087)	\$4,174	9.284 QALYs	\$71,416/QALY (26,916-171,866)
55 y	Comparison	\$2,171	6.381 QALYs		\$2,171	6.381 QALYs	
	Intervention	\$3,342	6.387 QALYs	\$199,505/QALY (101,956-408,299)	\$3,373	6.386 QALYs	\$259,286/QALY (93,039-1,505,203)
65 y	Comparison	\$3,573	10.695 QALYs		\$3,573	10.695 QALYs	
	Intervention	\$4,334	10.746 QALYs	\$15,051/QALY (6,565-25,105)	\$4,323	10.745 QALYs	\$14,959/QALY (5,982-27,693)
70 y	Comparison	\$3,215	8.911 QALYs		\$3,215	8.911 QALYs	
	Intervention	\$4,054	8.949 QALYs	\$22,390/QALY (10,671-36,820)	\$4,049	8.947 QALYs	\$22,900/QALY (9,929-42,908)
Participants with high risk for breast cancer with \geq 32% of energy from fat							
50 y	Comparison	\$7,884	9.183 QALYs		\$7,884	9.183 QALYs	
	Intervention	\$8,690	9.199 QALYs	\$51,698/QALY (8,776-235,507)	\$8,584	9.198 QALYs	\$47,112/QALY (4,561-256,084)
55 y	Comparison	\$5,211	6.339 QALYs		\$5,211	6.339 QALYs	
	Intervention	\$6,286	6.346 QALYs	\$153,460/QALY (0-1,323,115)	\$6,308	6.343 QALYs	\$267,985/QALY (0-3,574,977)
65 y	Comparison	\$7,549	10.413 QALYs		\$7,549	10.413 QALYs	
	Intervention	\$8,348	10.463 QALYs	\$15,786/QALY (5,198-39,143)	\$8,210	10.469 QALYs	\$11,687/QALY (2,627-29,658)
70 y	Comparison	\$6,826	8.695 QALYs		\$6,826	8.695 QALYs	
	Intervention	\$7,666	8.734 QALYs	\$21,659/QALY (6,970-63,163)	\$7,555	8.736 QALYs	\$17,730/QALY (4,435-54,343)
^a ICER=	^a ICER=incremental cost-effectiveness ratio.						
"Cl=confidence interval.							
~UALY=	=quality-adjusted	life vears.					

Sensitivity Analysis

Table 5 provides the results of a series of replications suggested in the literature. These replications evaluate the stability of the ICERs given changes in key model parameters and assumptions. Table 5 only provides the results for women with high fat intake at baseline (>36.8% of energy from fat), and who were aged 50 years at the beginning of intervention. Table 5 follows the societal perspective and uses the hazard ratios from randomization. The results for other age groups, perspectives and hazard ratios would parallel the results shown below.

The 20% reduction in the direct costs of the intervention reflects potential efficiency gains and cost-savings generated by implementing the intervention in a public health setting (41). This hypothetical reduction in costs generates significant changes in the societal perspective ICER.

For health care payers, the intervention costs would need to be reduced by 48% to be cost saving for Medicare and by 42% to be cost saving for private providers (calculations not shown).

An intervention with the characteristics of the WHI-DM, where most costs are realized early in the program, whereas the health outcomes accrue over many years, is likely to be sensitive to the discount rate. Table 5 confirms this expectation. The ICER is considerably lower when no discounting is performed (0% rate) and increased with the higher rate (5%). In the special case of 0% rate, the comparison case is dominated by the intervention, which provides stronger health outcome at a lower cost. Discounting health benefits for preventive measures is controversial, given the potential to excessively devalue downstream benefits (6).

Although the usual procedure is to use the average wage, it might overstate the opportunity costs of participants (42). The ICER presented in Table 5 (\$10,050/ QALY) indicates that the cost effectiveness of the WHI-DM is comparable to the lifestyle intervention in the Diabetes Prevention Program (\$8,800/QALY), where half of the wage was used to assess opportunity costs (41).

In the WHI-DM intervention, the average group size was 12 participants and the average research site had 456 participants. The results shown in Table 5 indicate that the intervention would remain cost-effective even if implemented with groups as small as six participants and in sites as small as 228 participants. These results provide further justification for applying the WHI-DM as a public health intervention, where it might not be feasible to enforce the 12 participants per group and 456 participants per site requirements.

DISCUSSION

From a societal perspective, the WHI-DM is associated with ICERs that are substantially lower than conventional thresholds and that are comparable with other preventive, nutrition-based interventions (43,44). For 50year-old women with >36.8% of energy from fat at baseline, the ICER is \$13,773/QALY, using hazard ratios from randomization. The intervention is also very cost-effective for women at high risk for breast cancer with $\geq 32\%$ of energy from fat. In this case, for 50-year-old women the ICER is \$10,544/QALY, using hazard ratios from inter-

Table 5. Sensitivity analysis for the Women's Health Initiative Randomized Controlled Dietary Modification Trial cost-effectiveness							
Group	Total cost	Effectiveness	ICER ^a (95% CI ^b)				
20% reduction in	direct costs						
Comparison	\$44,100	15.841 QALYs ^c					
Intervention	\$44,934	15.926 QALYs	\$9,873/QALY (4,591-15,902)				
0% discount rate							
Comparison	\$74,333	25.226 QALYs					
Intervention	\$73,745	25.414 QALYs	-\$3,083/QALY (-5,949-123)				
5% discount rate	•						
Comparison	\$33,352	12.371 QALYs					
Intervention	\$35,041	12.424 QALYs	\$31,939/QALY (22,124-43,890)				
Half of the hourly wage to measure opportunity cost							
Comparison	\$44,100	15.841 QALYs					
Intervention	\$44,949	15.926 QALYs	\$10,050/QALY (3,928-17,033)				
6 participants/group and 228 participants/site							
Comparison	\$44,100	15.841 QALYs					
Intervention	\$47,315	15.926 QALYs	\$38,034/QALY (26,159-51,415)				
^a ICER=incremental cost-effectiveness ratio. ^b CI=confidence interval. ^c QALY=quality-adjusted life years.							

vention. However, this result depends on accepting the first day of the nutrition intervention as the appropriate starting point for estimating hazard ratios.

An intervention similar to the WHI-DM would be an efficient use of Medicare resources, given the medical efficacy of the intervention in improving health outcomes and increasing quality of life. If only the direct costs to Medicare are considered, the ICER is \$15,051/QALY for 65-year-old women with high fat intake. These figures indicate that the WHI-DM features a similar cost and effectiveness profiles as other nutrition programs already adopted (15). Medicare currently covers medical nutrition therapy if the participant has diabetes or kidney disease (45). An expansion of the benefit to include women with high fat intakes as well as women with high risk for breast cancer is suggested by the current analysis.

Together with lower mortality and improvement in quality of life, a lower cancer incidence yields financial savings in the form of lower treatment costs. Because the duration of enrollment in private health insurance plans is relatively short for women in the age groups covered in this research, private payers would be reluctant to cover a preventive intervention similar to the WHI-DM that has substantial initial costs and delayed benefits. After age 65 years, essentially all Americans receive health care coverage through Medicare. A private health care payer would not benefit financially from the lower cancer treatment costs associated with the prevention program if these costs happen after the participant joined Medicare. The private payer would require that a return on the investment is realized before the participant turns age 65 years, which implies a timeframe of only 15 years for participants who start the program at age 50 years, and only 10 years for those who start at age 55 years. For instance, for 50-year-old women with high fat intake, the ICER is \$66,059/QALY, an incremental cost that is not expected to be recovered by cost-sharing strategies such as charging participation fees or higher insurance copayments. On the other hand, decision makers following the societal or Medicare perspective are not bound by the age 65 years deadline and they can/should assume a longer timeframe, until the expected end of life for participants. The WHI-DM is an example of a prevention strategy that is cost-effective to society, but does not have a positive short-term financial return for private payers (39). Methods to shift private health care payers' perspectives would probably require a change in Medicare law, to allow Medicare to pay some of the intervention costs during the 15-year period before participants reached age 65 years (10). Some of the features of the Patient Protection and Affordable Care Act, enacted on March 23, 2010, and discussed below, might change private payer perspective concerning preventive programs similar to the WHI-DM, especially the requirement that qualified health plans should provide preventive services rated highly by the US Preventive Services Task Force.

Although designed as a clinical trial, the WHI-DM is highly appropriate to serve as the basis for public health interventions. The sample of participants represented the population more likely to benefit from a lower-fat diet (1), besides being much larger than the typical clinical trial sample (46). Enrollment of racial/ethnic minority groups proportionate to the total minority population of women between ages 50 and 79 years was a high priority of the program. These special efforts overcome the usual under representation of minority groups in randomized controlled trials (47). The WHI study also had a much longer follow-up where the treatment effects were tracked in a more realistic period than the typical clinical trial of preventive interventions (44). The main limitation of this study is that it relies on the specific features of the WHI-DM study and, strictly speaking, the cost-effectiveness only pertains to interventions that follow identical design. In particular, the specific design of the medical nutrition therapy program offered by Medicare does not allow for a direct application of the ICERs presented above to this strategy. Specifically, the medical nutrition therapy benefit covers 3 hours of one-on-one counseling services with a registered dietitian or a qualified dietetics practitioner during the first year, and 2 hours each year after that if the nutrition therapy service is prescribed by a physician (48). This delivery method is quite distinct from the one used in the WHI-DM, which relies on more frequent sessions—18 in the first year—delivered to groups of participants. Nonetheless, the research indicates the benefit and cost-effectiveness of a low-fat diet intervention and it provides guidance to future applications.

Our cost-effectiveness analysis included only breast and ovarian cancer as the outcomes of interest because these were clearly established clinic benefits of the WHI-DM intervention. Other outcomes of the dietary modification trial were studied: colorectal cancer (49), cardiovascular disease (50), and cancer of the endometrium (3). The low-fat dietary intervention did not influence the incidences of colorectal cancer and stroke and it had no significant effect on the incidence of coronary heat disease and cancer of endometrium. Tinker and colleagues (51) indicated that the low-fat dietary pattern implemented in the WHI-DM showed no evidence of reducing diabetes risk after 8.1 years. For this reason, these outcomes are not included in our analysis. The intervention aimed to change diet patterns but did not encourage weight loss or energy reduction. Nevertheless, Howard and colleagues (52) reported that women in the intervention group lost weight during the first year (mean of 2.2) kg) and maintained lower weight than control women during an average 7.5 years of follow-up (difference 1.9 kg at 1 year and 0.4 kg at 7.5 years). This modest weight loss is not expected to yield any significant health benefit.

Some of the features of the Patient Protection and Affordable Care Act, enacted on March 23, 2010, have implications to the findings of this analysis. The act provides some emphasis to cost and premium reductions, especially upon the implementation of health insurance exchanges in 2014 (53). The act establishes the Patient-Centered Outcomes Research Institute to identify research priorities and conduct research that compares the clinical effectiveness of medical treatments, although cost-effectiveness is not explicitly mentioned. The more relevant features are the series of programs focused on prevention, including the National Prevention, Health Promotion, and Public Health Council, to coordinate federal prevention, wellness, and public health activities; Prevention and Public Health Fund to expand and sustain funding for prevention and public health programs; the task forces on Preventive Services and Community Preventive Services to develop, update, and disseminate evidenced-based recommendations on the use of clinical and community prevention services; the Prevention and Public Health Fund for prevention, wellness, and public health activities, including prevention research and health screenings; the grant program to support the delivery of evidence-based and community-based prevention and wellness service; the provision to eliminate costsharing for Medicare-covered preventive services that are recommended (rated A or B) by the US Preventive Services Task Force and the similar provision to provide incentives for states to eliminate cost-sharing for Medicaid-covered preventive services; to authorize Medicare coverage of personalized prevention plan services; to provide incentives to Medicare and Medicaid beneficiaries to complete behavior modification programs; to require qualified health plans to provide at a minimum coverage without cost-sharing for preventive services rated A or B by the US Preventive Services Task Force; and additional preventive care and screenings for women (54). The results of this cost-effectiveness analysis receive additional importance in this new health care context and they should receive specific consideration as these preventive programs are implemented.

CONCLUSIONS

The WHI-DM is a cost-effective strategy for the prevention of breast and ovarian cancer for the two groups in the target population of this study: women consuming >36.8% of energy from fat at baseline, and women at high risk for breast cancer consuming \geq 32% of energy from fat at baseline, from both societal and Medicare perspectives. The intervention is not cost-effective from a private health care payer perspective.

The cost-effectiveness analysis of the WHI-DM program assumes that a similar intervention could be implemented elsewhere and that similar outcomes would be achieved. Public health institutions, including government agencies, should consider the favorable ICERs reported here for decisions concerning preventive services initiatives and for recommendations about a lower-fat diet as a preventive strategy for breast and ovarian cancers for women with similar profiles as the target population used in this study. Likewise, Medicare should consider expanding the medical nutrition therapy program to include women with high fat intakes or high risk for breast cancer. Researchers are encouraged to use costeffectiveness analysis in the identification of beneficial nutrition interventions and, more broadly, beneficial preventive programs.

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References

- Ritenbaugh C, Patterson RE, Chlebowski RT, Caan B, Fels-Tinker L, Howard B, Ockene J. The Womens Health Initiative dietary modification trial: Overview and baseline characteristics of participants. *Ann Epidemiol.* 2003;13(suppl 9):S87-S97.
- Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, Margolis KL, Limacher MC, Manson JE, ParkerLM, Paskett E, Phillips L, Robbins J, Rossouw JE, Sarto GE, Shikany JM, Stefancik ML, Thomson CA, Van Horn L, Vitolins MZ, Wactawski-Wende J, Wallance RB, Wassertheil-Smoller S, Whitlock E, Yano K, Adams-Campbell L, Anderson GL, Assaf AR, Beresford SA, Black HR, Brunner RL, Bryzki RG, Ford L, Gass M, Hays J, Heber D, Heiss G, Hendrix SL, Hsia J, Hubbell FA, Jackson RD, Johnson KC, Kotchen

JM, LaCroix AZ, Lane DS, Langer RD, Lasser NL, Henderson MM. Low-fat dietary pattern and risk of invasive breast cancer: The Women's Health Initiative randomized controlled dietary modification trial. *JAMA*. 2006;295:629-642.

- Prentice RL, Thomson CA, Caan B, Hubbell FA, Anderson GL, Beresford SA, Pettinger M, Lane DS, Lessin L, Yasmeen S, Singh B, Khandekar J, Shikany JM, Satterfield S, Chlebowski RT. Low-fat dietary pattern and cancer incidence in the Women's Health Initiative dietary modification randomized controlled trial. J Natl Cancer Inst. 2007;99:1534-1543.
- 4. Russell LB, Siegel JE, Daniels N, Gold MR, Luce BR, Mandelblatt JS. Cost-effectiveness analysis as a guide to resource allocation in health: Rules and limitations. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. Cost-Effectiveness in Health and Medicine. New York, NY: Oxford University Press; 1996:3-24.
- Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. Cost-Effectiveness in Health and Medicine. New York, NY: Oxford University Press; 1996.
- Drummond MF, O'Brien BJ, Stoddart G, Torrance G. Methods for the Economic Evaluation of Health Care Programmes. 2nd ed. Oxford, UK: Oxford University Press; 1997.
- Garber AM, Weinstein MC, Torrance GW, Kamlet MS. Theoretical foundations of cost-effectiveness analysis. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. Cost-Effectiveness in Health and Medicine. New York, NY: Oxford University Press; 1996:25-53.
- Lipscomb J, Weinstein MC, Torrance GW. Time preference. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996: 214-246.
- Johannesson M, Jonsson B, Jonsson L, Kobelt G, Zethraeus N. Why should economic evaluations of medical innovations have a societal perspective? Office Health Econ Res Brief. 2009;51:1-32.
- Ackermann RT, Marrero DG, Hicks KA, Hoerger TJ, Sorensen S, Zhang P, Engelgau MM, Ratner RE, Herman WH. An evaluation of cost sharing to finance a diet and physical activity intervention to prevent diabetes. *Diabetes Care*. 2006;29:1237-1241.
- Chapman RH, Berger M, Weinstein MC, Weeks JC, Goldie S, Neumann PJ. When does quality-adjusting life-years matter in cost-effectiveness analysis. *Health Econ*. 2004;13:429-436.
- Grosse SD, Teutsch SM, Haddix AC. Lessons from cost-effectiveness research for United States Public Health Policy. Annu Rev Public Health. 2007;28:365-391.
- Braithwaite RS, Meltzer DO, King JT Jr, Leslie D, Roberts MS. What does the value of modern medicine say about the \$50,000 per qualityadjusted life-year decision rule? *Med Care*. 2008;46:349-356.
- Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality-adjusted life year: In search of a standard. *Med Decis Making*. 2000;20:332-342.
- Institute of Medicine. Committee on Nutrition Services for Medicare Beneficiaries. The Role of Nutrition in Maintaining Health in the Nation's Elderly. Evaluating Coverage of Nutrition Services for the Medicare Population. Washington, DC: National Academies Press; 2000.
- Briefing paper for the methods working party on the cost effectiveness threshold. 2007. National Institute for Health and Clinical Excellence Web site. http://www.nice.org.uk. Accessed June 12, 2010.
- Sonnenberg FA, Beck JR. Markov models in medical decision making: A practical guide. *Med Decis Making*. 1993;13:322-338.
- Anderson K, Jacobson JS, Heitjan DF, Zivin JG, Hershman D, Neugut AI, Grann VR. Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation. *Ann Intern Med.* 2006; 144:397-406.
- Grann VR, Jacobson JS, Whang W, Hershman D, Heitjan DF, Antman KH, Neugut AI. Prevention with tamoxifen or other hormones versus prophylactic surgery in BRCA1/2-positive women: A decision analysis. *Cancer J Sci Am.* 2000;6:13-20.
- Griffith GL, Edwards RT, Gray J, Wilkinson C, Turner J, France B, Bennett P. Estimating the survival benefits gained from providing national cancer genetic services to women with a family history of breast cancer. Br J Cancer. 2004;90:1912-1919.
- Melnikow J, Kuenneth C, Helms LJ, Barnato A, Kuppermann M, Birch S, Nuovo J. Chemoprevention: Drug pricing and mortality—The case of tamoxifen. *Cancer*. 2006;107:950-958.
- Noe LL, Becker RV, Gradishar WJ, Gore M, Trotter JP. The cost effectiveness of tamoxifen in the prevention of breast cancer. Am J Managed Care. 1999;5(suppl):S389-S406.
- Stout NK, Rosenberg MA, Trentham-Dietz A, Smith MA, Robinson SM, Fryback DG. Retrospective cost-effectiveness analysis of screening mammography. J Natl Cancer Inst. 2006;98:774-782.

- 24. Gorbach SL, Morrill-LaBrode A, Woods MN, Dwyer JT, Selles WD, Henderson M, Insull W Jr, Goldman S, Thompson D, Clifford C. Changes in food patterns during a low-fat dietary intervention in women. J Am Diet Assoc. 1990;90:802-809.
- Buzzard IM, Asp EH, Chlebowski RT, Boyar AP, Jeffery RW, Nixon DW, Blackburn GL, Jochimsen PR, Scanlon EF, Insull W Jr. Diet intervention methods to reduce fat intake: Nutrient and food group composition of self-selected low-fat diets. J Am Diet Assoc. 1990;90: 42-49.
- Miller DK, Homan SM. Determining transition probabilities: Confusion and suggestions. Med Decis Making. 1994;14:52-58.
- Hulka BS, Moorman PG. Breast cancer: Hormones and other risk factors. *Maturitas*. 2001;38:103-113.
- Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19:61-109.
- Tinker L, Burrows E, Henry H, Patterson R, Rupp J, Van Horn L. The Women's Health Initiative: Overview of the nutrition components. In: Krummel DA, Kris-Etherton PM, eds. Nutrition in Women's Health. Gaithersburg, MD: Aspen Publishers; 1996:510-549.
- Highlights of Women's Earnings in 2008. Bureau of Labor Statistics Web site. http://www.bls.gov/cps/cpswom2008.pdf. Accessed November 26, 2009.
- Usual Weekly Earnings of Wage and Salary Workers News Release, July 17, 2008. Bureau of Labor Statistics Web site. http://www.bls. gov/news.release/archives/wkyeng_07172008.htm. Accessed January 23, 2009.
- Occupational Employment and Wages, May 2008. Bureau of Labor Statistics Web site. http://www.bls.gov/oes/2008/may/oes291031.htm. Accessed January 23, 2009.
- 33. American Dietetic Association's 2005 Dietetics Compensation and Benefits Survey. American Dietetic Association Web site. http://www. eatright.org/cps/rde/xchg/ada/hs.xsl/career_1832_ENU_HTML.htm. Accessed January 23, 2009.
- 2001-02 CNPP Prices Database. Beltsville, MD: US Department of Agriculture, Center for Nutrition Policy and Promotion; 2008.
- Tinker LF, Rosal MC, Young AF, et al. Predictors of dietary change and maintenance in the Women's Health Initiative Dietary Modification Trial. J Am Diet Assoc. 2007;107:1155-1166.
- 36. Mossavar-Rahmani Y, Henry H, Rodabough R, Bragg C, Brewer A, Freed T, Kinzel L, Pedersen M, Soule CO, Vosburg S. Additional self-monitoring tools in the dietary modification component of the Women's Health Initiative. J Am Diet Assoc. 2004;104:76-85.
- Tinker LF, Patterson RE, Kristal AR, Bowen DJ, Kuniyuki A, Henry H, Shattuck A. Measurement characteristics of 2 different self-monitoring tools used in a dietary intervention study. J Am Diet Assoc. 2001;101:1031-1040.
- Fireman BH, Quesenberry CP, Somkin CP, Jacobson AS, Baer D, West D, Potosky AL, Brown ML. Cost of care for cancer in a health maintenance organization. *Health Care Financ Rev.* 1997;18:51-76.
- Yabroff KR, Lamont EB, Mariotto A, Warren JL, Topor M, Meekins A, Brown ML. Cost of care for elderly cancer patients in the United States. J Natl Cancer Inst. 2008;100:630-641.
- Greenberg D, Earle C, Fang CH, Eldar-Lissai A, Neumann PJ. When is cancer care cost-effective? A systematic overview of cost-utility analyses in oncology. J Natl Cancer Inst. 2010;102:82-88.
- 41. Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, Zhang P, Hamman RF, Ackermann RT, Engelgau MM, Ratner DE; Diabetes Prevention Program Research Group. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. Ann Intern Med. 2005;142: 323-332.

- 42. Luce BR, Manning WG, Siegel JE, Lipscomb J. Estimating costs in cost-effectiveness analysis. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996:176-213.
- Pavlovich WD, Waters H, Weller W, Bass EB. Systematic review of literature on the cost-effectiveness of nutrition services. J Am Diet Assoc. 2004;104:226-232.
- 44. Avenell A, Broom J, Brown T J, Poobalan A, Aucott L, Stearns SC, Smith WC, Jung RT, Campbell MK, Grant AM. Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. *Health Technol Assess.* 2004;8:iii-iv1-182.
- Lesse LI, Bazemore AW. Improving the delivery of preventive services to Medicare beneficiaries. JAMA. 2009;302:2699-2700.
- Hays J, Hunt JR, Hubbell A, Anderson GL, Limacher M, Allen C, Rossouw JE. The Women's Health Initiative recruitment methods and results. *Ann Epidemiol*. 2003;13(suppl 9):S18-S77.
- 47. Mandelblatt JS, Fryback DG, Weinstein MC, Russell LB, Gold MR, Hadorn DC. Assessing the effectiveness of health interventions. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996:135-175.
- Medical Nutrition Therapy services overview. Center for Medicare and Medicaid Services Web site. http://www.cms.gov/MedicalNutrition Therapy. Accessed June 10, 2010.
- 49. Beresford SAA, Johnson KC, Ritenbaugh C, Lasser NL, Snetselaar LG, Black HR, Anderson GL, Assaf AR, Bassford T, Bowen D, Brunner RL, Brzyski RG, Caan B, Chlebowski RT, Gass M, Harrigan RC, Hays J, Heber D, Heiss G, Hendrix SL, Howard BV, Hsia J, Hubbell FA, Jackson RD, Kotchen JM, Kuller LH, LaCroix AZ, Lane DS, Langer RD, Lewis CE, Manson JE, Margolis KL, Mossavar-Rahmani Y, Ockene JK, Parker LM, Perri MG, Phillips L, Prentice RL, Robbins J, Rossouw JE, Sarto GE, Stefanick ML, Van Horn L, Vitolins MZ, Wactawski-Wende J, Wallace RB, Whitlock E. Low-fat dietary pattern and risk of colorectal cancer: The Women's Health Initiative randomized control dietary modification trial. JAMA. 2006;295:643-654.
- 50. Howard BV, Horn LV, Hsia J, Manson JE, Stefanick ML, Wassertheil-Smoller S, Kuller LH, LaCroix AZ, Langer RD, Lasser NL, Lewis CE, Limacher MC, Margolis KL, Mysiw WJ, Ockene JK, Parker LM, Perri MG, Phillips L, Prentice RL, Robbins J, Rossouw JE, Sarto GE, Schatz IJ, Snetselaar LG, Stevens VJ, Tinker LF, Trevisan M, Vitolins MZ, Anderson GL, Assaf AR, Bassford T, Beresford SA, Black HR, Brunner RL, Brzyski RG, Caan B, Chlebowski RT, Gass M, Granek I, Greenland P, Hays J, Heber D, Heiss G, Hendrix SL, Hubbell FA, Johnson KC, Kotchen JM. Low-fat dietary pattern and risk of cardiovascular disease: The Women's Health Initiative randomized controlled dietary modification trial. JAMA. 2006;295:655-666.
- 51. Tinker LF, Bonds DE, Margolis KL, Manson JE, Howard BV, Larson J, Perri MG, Beresford SA, Robinson JG, Rodriguez B, Safford MM, Wenger NK, Stevens VJ, Parker LM. Low-fat dietary pattern and risk of treated diabetes mellitus in postmenopausal women: The Women's Health Initiative randomized controlled dietary modification trial. Arch Intern Med. 2008;168:1500-1511.
- Howard BV, Manson JE, Stefanick ML. Low fat dietary pattern and weight change over 7 years: The Women's Health Initiative dietary modification trial. JAMA. 2006;295:39-49.
- Focus on Health Reform: Health Reform Implementation Timeline. Menlo Park, CA: Henry J Kaiser Family Foundation; 2010.
- Focus on Health Reform: Summary of the New Health Reform Law. Menlo Park, CA: Henry J. Kaiser Family Foundation; 2010.