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Strategies for Recruitment to a Population-based Lung Cancer Prevention Trial: The CARET Experience with Heavy Smokers[1]

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Abstract

The Beta-Carotene and Retinol Efficacy Trial tested the effect of the combination of β-carotene (30 mg) and retinyl palmitate (25,000 units) daily on the incidence of lung cancer in high-risk individuals. In study centers located in Seattle, WA; Portland, OR; and Irvine, CA, we recruited current and recent ex-cigarette smokers, aged 50–69 years. Our primary method of recruitment was by mailing study information and eligibility questionnaires to age-selected health insurance subscribers. A total of 1,216,549 subscriber households were contacted, which resulted in 16,449 enrollments and 12,184 randomizations. Other methods of recruitment yielded 1421 enrollments and 1002 randomizations. Seventy-four % of those participants who enrolled in the 3-month placebo run-in were randomized. The major reasons for nonrandomization once subjects were enrolled were: becoming ineligible (13%), concern about or development of side effects attributed to the study vitamins (18%), loss of interest or being too busy (23%), and not showing up at the appointed time or not willing to come to the study center (23%). Here, we discuss the reasons for nonparticipation and for subjects leaving the trial prior to randomization and possible modifications of trial design and procedures to address these problems. This recruitment approach provided a constant flow of potentially eligible participants, screened out many ineligible and uninterested persons prior to the scheduling of a study center visit, and ensured randomization of committed participants. A major limitation of this study was that the pool of minorities that was reached was small.

Introduction

Large-scale human cancer prevention trials with the end point of cancer incidence are the gold standard for testing scientific and public health hypotheses arising from observational epidemiological, animal, and *in vitro* studies of dietary micronutrients, vitamins, and other potential chemoprevention agents.

Recruitment to this type of disease prevention trial presents a major challenge. In contrast to treatment trials in patients diagnosed with cancer, primary prevention trials seek to enroll healthy participants who may not be receiving routine medical care and, therefore, cannot be recruited via the usual clinical trial methods of direct physician contact. In addition, primary prevention trials require long-term adherence to an intervention regimen to achieve adequate statistical power to detect a statistically significant reduction (or increase) in incidence rates. Poor recruitment results or an unexpectedly high dropout rate can preclude successful completion of the trial.

In 1985, we began recruitment to a cancer prevention trial in the largest clearly identifiable population at high risk for lung cancer, current and former heavy cigarette smokers. No cancer prevention trial in this population had previously been attempted in this country.

Here, we present the methods used to recruit this population to the CARET,[3] the results and the reasons given by participants who left the trial prior to being randomized. Analyses of factors influencing retention rates over the follow-up periods exceeding 10 years will be reported separately.

Materials and Methods

From 1985 to 1988, we conducted two pilot trials to test the feasibility of a lung cancer primary prevention trial with β-carotene and vitamin A in two healthy but high-risk populations: current or former cigarette smokers (1) and individuals with a history of occupational asbestos exposure (2). Because of the marked differences in the recruitment methods for the two high-risk populations, we will only discuss recruitment of the smoking population here. These pilot studies demonstrated successful recruitment, no toxicity, and high adherence to the regimen. In 1988, recruitment was expanded 10-fold to accrue sufficient participants to test the effect of the combination of these two agents on the incidence of lung cancer (3). The eligibility criteria for heavy smokers included: males and

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[3] The abbreviations used are: CARET, Beta-Carotene and Retinol Efficacy Trial; HMO, health maintenance organization; AARP, American Association of Retired Persons; ATBC, Alpha-Tocopherol Beta-Carotene.

females, aged 50–69 years, with a smoking history of 20 pack-years or greater, who were current smokers or recent ex-smokers (no more than 6 years since they had stopped). Participants were excluded if they had a history of cancer within 5 years or a diagnosis of cirrhosis. Active intervention was terminated in January 1996 after an interim analysis found evidence of no benefit and substantial evidence of harm (increased incidences of lung cancer and total mortality; Refs. 4 and 5).

Here, we focus on the 13,186 participants randomized at the three largest CARET study centers: the Fred Hutchinson Cancer Research Center in Seattle, Washington; the Kaiser Permanente Center for Health Research in Portland, Oregon; and the University of California Medical Center at Irvine, California.

Direct Mail Recruitment. Our initial and predominant method of recruitment was by direct mailing of information to potential participants' homes. Regional health insurance carriers were our first sources of the mailing lists used. In most instances, the medical directors of these programs were contacted and given detailed information on the trial. After an internal discussion and general agreement, our proposed recruitment materials were reviewed and modified by the public relations and legal departments of each health care provider. The Washington State insurers who participated were: Blue Shield in King, Pierce, and Snohomish Counties (Western Washington); Blue Cross of Washington and Alaska; and two Washington HMOs, Group Health Cooperative of Puget Sound and Pacific Medical Center Cooperative. The insurance carriers participating in Oregon were Blue Cross/Blue Shield and three HMOs: Kaiser Permanente (Northwest Division), Capital Health Care, and Sisters of Providence/Good Health Plan. Those participating in southern California were Blue Cross/Blue Shield and two HMOs: Kaiser Permanente (southern California Division) and Health Net. None of the insurers approached refused to participate.

Each of the providers scanned its membership roles for subscribers in the eligible age range (50–69 years). This was the only cost-generating activity required of insurers. Recruitment packets were mailed by the study centers to the household address of each of these subscribers. An introductory letter was printed on the health care provider's stationery and signed by the company's medical director, explaining that participation in the trial was an individual decision. This letter was mailed with the following: a one-page letter from the study investigators explaining the background, rationale, and outline of the trial; two one-page questionnaires to determine eligibility and potential interest (for the subscriber and a potentially eligible housemate); and a postpaid return envelope. To maintain confidentiality, two insurers required they conduct all processing and mailing of recruitment packets.

In general, each study center mailed recruitment packets in weekly batches of 5,000–10,000. Returned questionnaires were reviewed to determine eligibility. The Portland Study Center sent a reminder postcard after 2 weeks and a second packet to households who did not return a questionnaire within 1 month. Most mailings were sent by first-class mail. To test relative costs and effectiveness, we sent some by first-class and some by bulk mail. These results are reported elsewhere (6). Each study center reviewed the returned interest surveys and screened out those who were ineligible because of age or lack of sufficient smoking history. Study centers telephoned all individuals who returned the screening questionnaire except those who were clearly ineligible. The purpose of the phone call was to review or clarify information on the interest survey, confirm eligibility, and schedule an appointment for the first study center visit. All activity through the first appointment is called recruitment.

Other Recruitment Sources. We contacted the national offices of the AARP as a recruitment source. As an advocate for individuals over the age of 50, this national organization appeared to be ideal for recruiting healthy participants to prevention trials. Participation by AARP required review and approval of both the protocol and the consent form by the AARP scientific and executive boards, as well as by their legal advisers. CARET was the first trial to be given approval to recruit from regional AARP membership rolls. Recruitment methods were similar to that used with the health insurers, including a letter from a national officer of AARP. A limited number of mailings were sent to the AARP members in Washington and Oregon because approval from AARP was obtained close to the completion of recruitment at these study centers. In contrast, the AARP mailing list was used more extensively at the Irvine Study Center.

Seattle and Portland have large military bases in their surrounding communities. Associated with these bases are large numbers of retired military personnel. We contacted the local retirement organizations of the Army, Air Force, Navy, and Coast Guard to recruit their age-eligible retirees. All agreed to send a reformatted recruitment letter and packet.

In both Washington and Oregon, the American Lung Association has support groups for individuals with chronic lung diseases and/or those who wish to stop smoking (the "Lung Club" or "Better Breathers Club"). The American Lung Association provided a mailing list so that these members could receive a recruitment packet.

The Portland Study Center tested a pilot mailing to 6000 random age-eligible individuals from a mailing list of registered motorists available from the State of Oregon and a list of "smokers/blue collar workers" purchased from Polk Direct Mail Advertising Company (Atlanta, GA). The latter list of smokers is available by zip codes and occupation categories. The Portland Study Center had access to two other local groups, smokers enrolled previously in a smoking cessation study within the Kaiser Permanente system and interested but ineligible respondents for the Oregon Health Sciences University Lung Health Study. The objective of both studies was to increase ex-smoker rates. Neither study involved a pharmacological intervention agent. Both groups were sent CARET recruitment packets.

Nondirected Mail Recruitment. In Washington, we attempted recruitment via Val-Pak, a commercial company that distributes store coupons and general advertising each month via the United States Postal Service. For marketing purposes, the Puget Sound region has been divided into geographic blocks of 10,000 households. For each of these blocks, demographic information (average income, age, sex, and ethnic composition) is available. We reformatted our recruitment letter and questionnaire to a single page with a tear off return mailer and selected blocks with a high percentage of residents over age 50 and a high percentage of ethnic minorities. Recruitment forms were distributed as part of the Val-Pak mailing in May 1992 (20,000 households), July 1992 (20,000 households), and September 1992 (40,000 households).

In the Puget Sound region, the yearly home delivery of telephone books is accompanied by advertisement flyers and coupons. Our recruitment letter and mail-back form (formulat-

Table 1 Recruitment results using direct mail contact, by source[a]

	No. of households contacted	Questionnaires returned	No. returned per 100 households contacted	Eligible and interested		Enrolled		Randomized participants	
				No.	%	No.	%	No.	No. per 100 households contacted
Washington									
Blue Shield									
King County	79,689	8,799	11	3,511	40	1,659	47	1,257	1.6
Pierce County	14,154	1,402	10	777	55	418	54	326	2.3
Snohomish County	11,243	1,394	12	595	43	208	35	156	1.4
Blue Cross of Washington	49,668	3,030	6	868	29	649	75	484	1.0
Group Health Cooperative-HMO	88,971	11,273	13	3,631	32	1,735	48	1,386	1.6
Pacific Medical Center-HMO	21,937	1,497	7	766	51	403	53	327	1.5
AARP	18,171	685	4	269	39	146	54	118	0.6
Army retirees	27,941	2,842	10	982	35	409	42	322	1.2
Air Force retirees	8,500	431	5	150	35	81	54	68	0.8
Coast Guard retirees	1,210	135	11	46	34	21	46	11	0.9
American Lung Association	1,800	100	6	32	32	16	50	7	0.4
Subtotal/average	323,284	31,588	10	11,627	37	5,745	49	4,462	1.4
Oregon									
Blue Cross/Blue Shield-Oregon	57,621	10,662	19	2,414	23	1,205	50	857	1.5
Kaiser Permanente	88,966	24,756	28	5,176	21	3,088	60	2,205	2.5
Capital HealthCare-HMO	10,732	2,112	20	347	16	108	31	82	0.8
Group Health Plan-HMO	12,193	2,269	19	610	27	168	28	110	0.9
AARP	27,499	1,399	5	461	33	208	45	146	0.5
Military retirees	1,790	325	18	140	43	77	55	52	2.9
American Lung Association	547	58	11	16	28	13	81	6	1.1
Stop Smoking Group	2,595	275	11	100	36	45	45	36	1.4
Lung Health Research Study	2,662	387	15	192	50	84	44	62	2.3
Smoker/blue collar workers mail list	48,059	2,883	6	589	20	280	48	196	0.4
Department of motor vehicles	6,000	259	4	76	29	29	38	21	0.4
Subtotal/average	258,664	45,385	18	10,121	22	5,305	52	3,773	1.5
California									
Blue Cross/Blue Shield of California	76,823	8,680	11	2,452	28	917	37	684	0.9
Kaiser Permanente	269,503	28,172	10	6,972	25	2,498	36	1,810	0.7
Health Net-HMO	92,480	6,754	7	2,157	32	872	40	684	0.7
AARP	195,795	6,637	3	2,356	35	1,112	47	771	0.4
Subtotal/average	634,601	50,243	8	13,937	28	5,399	39	3,949	0.6
Grand total/average	1,216,549	127,216	10	35,685	28	16,449	46	12,184	1.0

ed for Val-Pak) was included with telephone books delivered to 11,000 households in areas with high percentages of minorities.

We tested the feasibility of using published advertising as a recruitment source with the Group Health Cooperative monthly magazine. This magazine is distributed to the 170,000 Cooperative members (readership of 300,000) in the Puget Sound region. CARET purchased the back page for the months of December 1989 and March 1990, as our initial attempt at recruitment from Group Health Cooperative. This full-page advertisement included information about CARET and a "cut-out and mail-back" recruitment questionnaire. Separate advertised recruitment was attempted via a one-page insert that accompanied the grocery store advertising section of the weekly Seattle newspapers. We also placed informative posters about CARET with tear-off post cards in local pharmacies and physicians' offices.

In Portland, we sent letters asking participants to "recruit a buddy." Posters with tear off postcards requesting information on CARET were placed in area pharmacies and physicians' offices. Recruitment was attempted through the outreach network of occupational health nurses in the African-American community, as well as through local church groups.

Finally, in all study centers, participants were recruited via news media coverage in the form of articles in local newspapers, radio and television interviews, and, in Portland, paid newspaper and radio advertisements.

Enrollment, Placebo Run-in, and Randomization. The enrollment process for CARET began with the first study center visit. Baseline data were collected, eligibility was confirmed, and placebo capsules were dispensed to all participants. The enrollment phase continued until an individual was randomized (at the second visit), declined to participate before randomization, or was found to be ineligible. Three months (or up to a maximum of 6 months) after the enrollment visit, participants returned for a second visit, at which time study center staff re-reviewed eligibility. Eligible participants who had taken at least 50% of their study vitamins and were willing to continue in the study were then randomized.

Results

Recruitment by Source. Recruitment results based on the mailing of recruitment packets to individuals from various recruitment sources are presented in Table 1. CARET Study Centers contacted a total of 1,216,549 households via direct mail and from these households randomized 12,184 individuals, resulting in a randomization rate of 1.0 per 100 households contacted by mail. The rates were higher in both Oregon (1.5/

Table 2 Recruitment from other sources

	Estimated population reached	No. responding	No. eligible	No. enrolled	No. randomized
Washington					
Nondirect mail or distribution	91,000	210	112	42	32
Print media					
Seattle Scanner newspaper advertisement	20,000	0	0	0	0
Seattle Chinese Post advertisement	10,000	0	0	0	0
Seattle Post-Intelligencer article	207,299			2	2
Safeway advertisement	663,885	16	6	7	6
View magazine (Group Health Cooperative)	300,000	251	134	89	64
Radio news feature advertisement		1	0	0	0
Television news feature		53	18	0	0
Other				170	139
Oregon					
Community posters		136	91	77	57
Department of Motor Vehicle mailing	6,000	128	60	35	24
Print/radio news feature		1,662	920	566	370
Other				54	33
California					
Direct mail or distribution				58	41
Print news feature				176	132
Radio news feature				34	21
Television news feature				36	27
Other				75	54

100) and Washington (1.4/100) than in California (0.6/100). The highest recruitment yield from a major recruitment source was Kaiser Permanente in Portland (2.5 per 100 households contacted). We sent recruitment packets to 241,465 members of AARP; 8,721 individuals returned questionnaires (3.6 per 100 households), of whom 1,035 (0.4 per 100 households) were randomized.

Among all three study centers, we received 10.5 returned questionnaires per 100 households contacted. Of those who returned questionnaires, 35,685 (28%) appeared to be eligible and interested; of these, 16,449 (46%) had a first study center visit. Seventy-four % of those who had a first visit (12,184) were eventually randomized.

Table 2 shows recruitment and enrollment rates for nondirected mail sources. Advertisement in the Group Health Cooperative subscriber magazine, which has a distribution of 300,000 subscriber households, resulted in only 251 returned coupons; 134 of these were eligible (53%) and 64 were randomized (25%). Other sources of advertising recruitment (Table 2) were less successful, yielding only eight randomized participants in Washington state. The Portland Study Center worked intensively with the print, radio, and television media when the trial started. In response to this publicity, 1662 interested individuals telephoned the study center. A total of 370 (22%) were randomized. The Irvine Study Center randomized 132 participants who contacted the Center in response to print advertising.

Enrollment and Randomization. Among the three study centers, 9713 men and 8157 women came to the study center and completed a first visit. At that visit, 1726 dropped out and did not continue the enrollment process. After the ensuing 3-month placebo run-in period, an additional 2958 dropped out and were not randomized. The reasons for these dropouts are listed in Table 3.

The most common reason for not being randomized was ineligibility. Of the 4684 participants who dropped out during the enrollment process, 946 were found to not fit the eligibility criteria at the first visit; an additional 388 were found to be ineligible by the time of the randomization visit. In addition, 505 or 11% of participants decided not to participate in CARET explicitly because they wanted to take supplemental β-carotene or more than 5500 units/day of supplemental vitamin A, making them ineligible.

There were major differences in the reasons participants gave for leaving the study at the first visit compared to during or at the completion of the placebo run-in. At the first visit, 260 individuals declined to join the study because of concerns about side effects highlighted in the informed consent, compared with 107 who gave this as a reason for leaving the study after the run-in. At the conclusion of the placebo run-in, 403 (14%) left the study because of side effects that the participants attributed to β-carotene and retinol. After joining the study, many participants appear to have decided that participation was too much of a time commitment. At the first visit, participants stated they were too busy 16 times, were not willing to come to the study center 35 times, and were not (or were no longer) interested 40 times. At the second visit, these figures increased to 331, 301, and 350, respectively.

Among the three study centers, there was little variation in the reasons why participants left the trial. Although not statistically significant, Irvine had fewer ineligible participants compared with Washington and Oregon; 21, 29, and 35% of nonrandomized participants, respectively. In addition, the Irvine Study Center was actively recruiting at the time the ATBC trial published their results (7). This Finnish trial in high-risk smokers (a population similar to that recruited to CARET) reported that β-carotene supplements were associated with an 18% increased incidence in lung cancer. We sent letters to each CARET participant just before publication of the ATBC results and reminded them of their right to withdraw. Over a 4-month time period, 74 of 5,777 enrolled (but not yet randomized) participants in the California study center stopped taking CARET capsules, citing the results of the Finland trial as their reason.

To determine whether there were differences in retention rates between recruitment sources, we evaluated the number of randomized participants actively taking the intervention agents at 24 and 48 months. There were no statistically significant

Table 3 Reasons for dropout at first visit to study center and after placebo run-in (second visit)

	Washington		Oregon		California		Total	
	First visit	Second visit	First visit	Second visit	First visit	Second visit	First visit	Second visit
Number of dropouts[a]	460 (34%)	890 (66%)	965 (54%)	815 (46%)	301 (19%)	1253 (81%)	1726 (37%)	2958 (63%)
Reason for dropout[b]								
Ineligible	286 (62%)	101 (11%)	519 (54%)	108 (13%)	141 (47%)	179 (14%)	946 (55%)	388 (13%)
Afraid of developing side effects	68 (15%)	26 (3%)	154 (16%)	34 (4%)	38 (13%)	47 (4%)	260 (15%)	107 (4%)
Concerned about monitored symptoms or signs that have developed	0 (0%)	56 (6%)	0 (0%)	62 (8%)	0 (0%)	52 (4%)	0 (0%)	170 (6%)
Concerned about nonmonitored symptoms or signs that have developed	0 (0%)	72 (8%)	0 (0%)	75 (9%)	0 (0%)	86 (7%)	0 (0%)	233 (8%)
Other health problems	31 (7%)	94 (11%)	87 (9%)	81 (10%)	11 (4%)	101 (8%)	129 (7%)	276 (9%)
Emotional problems but not grade 5 anxiety/depression[c]	15 (3%)	23 (3%)	37 (4%)	18 (2%)	7 (2%)	26 (2%)	59 (3%)	67 (2%)
Taking too many medications	4 (1%)	8 (1%)	1 (<1%)	8 (1%)	1 (<1%)	9 (1%)	6 (<1%)	25 (1%)
Advised not to participate by personal physician or study center principal investigator	0 (0%)	34 (4%)	8 (1%)	35 (4%)	3 (1%)	58 (5%)	11 (1%)	127 (4%)
Wanted to take β-carotene or vitamin A over limit	64 (14%)	75 (8%)	143 (15%)	63 (8%)	49 (16%)	111 (9%)	256 (15%)	249 (8%)
Nonadherent to taking pills	2 (<1%)	69 (8%)	11 (1%)	57 (7%)	2 (1%)	71 (6%)	15 (1%)	197 (7%)
Physical trouble taking pills	0 (0%)	8 (1%)	4 (<1%)	4 (<1%)	2 (1%)	12 (1%)	6 (<1%)	24 (1%)
Did not like certain aspects of study	45 (10%)	73 (8%)	80 (8%)	48 (6%)	33 (11%)	83 (7%)	158 (9%)	204 (7%)
Not interested	7 (2%)	126 (14%)	17 (2%)	87 (11%)	16 (5%)	137 (11%)	40 (2%)	350 (12%)
No-show/out of window/unable to contact	1 (<1%)	78 (9%)	3 (<1%)	180 (22%)	0 (0%)	125 (10%)	4 (<1%)	383 (13%)
Not willing or unable to come to study center	8 (2%)	146 (16%)	21 (2%)	78 (10%)	6 (2%)	77 (6%)	35 (2%)	301 (10%)
Had moved or was moving soon	3 (1%)	34 (4%)	12 (1%)	21 (3%)	4 (1%)	43 (3%)	19 (1%)	98 (3%)
Too busy	3 (1%)	159 (18%)	10 (1%)	72 (9%)	3 (1%)	100 (8%)	16 (1%)	331 (11%)
ATBC[d] results	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	73 (6%)	1 (<1%)	73 (2%)
Death	0 (0%)	9 (1%)	0 (0%)	8 (1%)	0 (0%)	8 (1%)	0 (0%)	25 (1%)
Other or no reason given	14 (3%)	43 (5%)	49 (5%)	36 (4%)	23 (8%)	103 (8%)	86 (5%)	182 (6%)

[a] Percentages based on total number of nonrandomized individuals per study center.
[b] Some participants gave more than one reason. Percentages were based on total number of nonrandomized individuals per visit at each study center. Washington total does not include four participants who dropped out due to study center stopping randomization. California total does not include 21 participants who dropped out due to Safety and Endpoint Monitoring Committee stopping randomization.
[c] Symptom grading scale reported previously (1).
[d] ATBC trial reported adverse effect of β-carotene on lung cancer incidence in April 1994 (6).

differences between sources, although the Portland Kaiser Permanente population had the highest active rates at 88.5 and 81.9% at 24 and 48 months, respectively, whereas the rates in the population who joined the trial as a result of advertisement (print, radio, or television) had the lowest rates, at 80.1 and 76.7%, respectively.

We determined the costs of recruitment via our direct mail approach. As reported previously, a total of $442 was spent for each randomized participant (8). Because 92% of all smoking participants were reached via direct mail, we did not compare the costs for the different methods of recruitment.

Table 4 shows the characteristics of the 7426 male and 5760 female CARET participants randomized. The average age was 58 years. Ninety-four % were of European background, and 2% (217) had African heritage. Sixty-six % were current smokers, with a mean of 48 pack-years. Thirty-four % were ex-smokers with a smooth distribution of years since quit of 1–6 years. The ex-smokers had a mean smoking history of 52 pack-years.

Discussion

We were successful in the recruitment and randomization of a specific high-risk population (smokers and ex-smokers) through a direct mail strategy. The Physicians' Health Study (9) and The Women's Health Study (10) used a similar recruitment strategy by mailing recruitment letters to health care professionals. The prostate cancer prevention trial (11) and the breast cancer prevention trial (12, 13), conducted by the Southwest Oncology Group and the National Surgical Adjuvant Breast Project, respectively, recruited through their group members and their outreach programs, the Community Clinical Oncology Programs. These trials were also successful in recruiting and randomizing their projected accrual goals. Here, we provide the detailed results of our recruitment efforts, including the reasons participants gave when they chose not to join CARET. Our results, along with those of the other major trials, should allow others to better plan recruitment strategies for large-scale prevention trials.

There were differences in the rates of participants enrolled and randomized among recruitment sources and settings. Blue Cross/Blue Shield and their affiliates in Washington, Oregon, and California had rates of randomization of 1.6, 1.5, and 0.9 persons per 100 households contacted, respectively. The lower rate in California may reflect demographics that were specific to the health insurance population enrolled in California or temporal changes because the mailings in California took place in 1992–1994, an average of 3 years later than in Washington and Oregon. There was much more resistance to randomization to a placebo-controlled trial, presumably because of increased publicity and promotion of β-carotene during that interval.

Recruitment from HMOs did not appear to be better than from the general health-insured population. In Washington, the two participating HMOs randomized 1.6 and 1.5 persons per 100 households. However, Kaiser Permanente in Oregon randomized 2.5 per 100 households contacted. Recruitment rates in the California HMOs were much lower (0.7). It is likely that the higher recruitment rate in Oregon reflects the status of the Portland Study Center. The Center for Health Research in which the study center is located is organizationally and physically part of Kaiser Permanente and has a long tradition of

Table 4 Randomized participant characteristics

	Washington	Oregon	California	Total
Mean age (SD)				
Male	58 (6)	58 (5)	58 (6)	58 (6)
Female	57 (6)	58 (5)	58 (5)	58 (5)
Ethnic origin				
European	4,488 (95%)	4,144 (97%)	3,816 (90%)	12,446 (94%)
African	63 (1%)	31 (1%)	123 (3%)	217 (2%)
Hispanic	25 (1%)	23 (1%)	146 (3%)	193 (1%)
Asian	68 (1%)	21 (<1%)	77 (2%)	166 (1%)
Native American	42 (1%)	32 (1%)	27 (1%)	101 (1%)
Other/no response	19 (<1%)	6 (<1%)	35 (1%)	63 (<1%)
No. of current smokers	3,071 (65%)	2,936 (69%)	2,707 (64%)	8,714 (66%)
Mean pack-years (SD)	48 (19)	48 (19)	50 (20)	48 (19)
Number of ex-smokers	1,634 (35%)	1,321 (31%)	1,517 (36%)	4,472 (34%)
Years since quitting[a]				
<1	127 (8%)	152 (12%)	160 (11%)	439 (10%)
1	298 (18%)	214 (16%)	251 (17%)	763 (17%)
2	247 (15%)	230 (17%)	242 (16%)	719 (16%)
3	250 (15%)	224 (17%)	235 (16%)	709 (16%)
4	236 (14%)	183 (14%)	214 (14%)	633 (14%)
5	279 (17%)	227 (17%)	241 (16%)	747 (17%)
6	192 (12%)	90 (7%)	173 (11%)	455 (10%)
>6	5 (<1%)	1 (<1%)	1 (<1%)	7 (<1%)
Mean pack-years (SD)	52 (23)	51 (21)	53 (24)	52 (23)

[a] Percentages based on number of ex-smokers.

conducting health research among its members. Group Health Cooperative in Seattle maintains a similarly close research affiliation with its members. There is no doubt that the relationship between the recruiting organization and individual participants is important. Rather than receiving a letter from an insurance company or an institution with which they have no affiliation, participants may view a letter from their HMO as a credible incentive for improved health. Such experience may encourage the growing managed care sector to organize and cooperate with academic partners in prevention trials.

Recruitment from AARP was, in general, lower than that from other sources. In Washington and Oregon, the list provided by AARP was the last source used. It is certain that many AARP members had already been contacted through our other sources, and those interested in joining the trial had, presumably, been enrolled. Hence, recruitment in these states may underestimate the true utility of this source. However, in California, AARP was used for direct mail recruitment before other sources had been exhausted. From 195,795 packets mailed, the response rate was 3 persons per 100 households contacted, the lowest response rate seen from any source, and only 771 individuals were randomized (0.4%). Although recruitment rates in southern California via all sources were lower than those in Oregon and Washington, we have no reason to believe that AARP recruitment in the latter states would have been significantly better than the similar mailing to age-selected health insurance subscribers.

There were multiple attempts to recruit participants via printed advertising. The results of these efforts were poor, although it is our impression that concurrent advertising increased the rate of response to mailings, particularly second mailings. Radio and television news appearances were more successful. These efforts resulted in a small number of participants calling the study center, but among those, a high percentage were eligible and were eventually randomized. It is difficult to determine recruitment rates from these sources because the number of individuals contacted is unknown.

Twenty-six % of all participants (29% of female and 24% of male participants) who had a first visit to the study center were not randomized. We attempted to categorize reasons participants gave for leaving the study at the time of enrollment and during the placebo run-in because some of these reasons may be addressed by changes in study procedures or operations (Table 5). This approach has limitations, however, because the purpose of a placebo run-in is to identify participants who are unlikely to be adherent for the full duration of the trial and avoid their randomization.

Three hundred sixty-seven individuals were not randomized because they stated, at the first or second visit, that they feared side effects described in the consent form. An additional 403 participants left because of monitored or unmonitored symptoms or signs that developed during the placebo run-in that the participant attributed to the study vitamins (Table 5). Although it is essential to inform participants of the potential side effects of the agents being tested, a clearer discussion of the incidence and severity of potential side effects and symptoms may be useful. For example, participants were concerned and requested additional information about our warning for potential synergistic toxicity between vitamin A and alcohol. When we subsequently updated the consent form, we summarized results from the CARET pilot studies (1, 2), which showed no adverse interaction on liver function tests.

One hundred thirty-eight participants were not randomized because they stated they were advised by their personal physician not to participate in the study. However, on most occasions when personal physicians were contacted to discuss the trial, they expressed no concern about their patient's participation. Thus, the study interviewers felt that this explanation was often given by participants who did not want to continue in the trial. This loss might be reduced and subsequent retention be enhanced if, prior to recruitment, local physicians are notified of the rationale for the trial and the expected low incidence of side

Table 5 Reasons for nonrandomization

	Washington	Oregon	California	Total
Enrolled	6,055	6,037	5,777	17,870
Male	3,341	3,224	3,147	9,713
Female	2,714	2,813	2,630	8,157
No. of ineligibles/dropouts	1,350 (22%)	1,780 (30%)	1,554 (27%)	4,684
Male	666	856	765	2,287
Female	684	924	789	2,397
Age of dropouts (yr), mean (SD)	57 (5)	58 (5)	58 (6)	58 (5)
Reason for dropout[a]				
Ineligible	387 (29%)	627 (35%)	320 (21%)	1,334 (28%)
Afraid of developing side effects	94 (7%)	188 (11%)	85 (5%)	367 (8%)
Concerned about monitored symptoms or signs that have developed	56 (4%)	62 (3%)	52 (3%)	170 (4%)
Concerned about nonmonitored symptoms or signs that have developed	72 (5%)	75 (4%)	86 (6%)	233 (5%)
Other health problems	125 (9%)	168 (9%)	112 (7%)	405 (9%)
Emotional problems but not grade 5 anxiety/depression	38 (3%)	55 (3%)	33 (2%)	126 (3%)
Taking too many medications	12 (1%)	9 (<1%)	10 (1%)	31 (1%)
Advised not to participate by personal physician or study center principal investigator	34 (3%)	43 (2%)	61 (4%)	138 (3%)
Wanted to take β-carotene or vitamin A over limit	139 (10%)	206 (12%)	160 (10%)	505 (11%)
Nonadherent to taking pills	71 (5%)	68 (4%)	73 (5%)	212 (5%)
Physical trouble taking pills	8 (1%)	8 (<1%)	14 (1%)	30 (1%)
Did not like certain aspects of study	118 (9%)	128 (7%)	116 (7%)	362 (8%)
Not interested	133 (10%)	104 (6%)	153 (10%)	390 (8%)
No-show/out of window/unable to contact	79 (6%)	183 (10%)	125 (8%)	387 (8%)
Not willing or unable to come to study center	154 (11%)	99 (6%)	83 (5%)	336 (7%)
Had moved or was moving soon	37 (3%)	33 (2%)	47 (3%)	117 (2%)
Too busy	162 (12%)	82 (5%)	103 (7%)	347 (7%)
ATBC results	0 (0%)	0 (0%)	74 (5%)	74 (2%)
Death	9 (1%)	8 (<1%)	8 (1%)	25 (1%)
Other or no reason given	57 (4%)	85 (5%)	126 (8%)	268 (6%)

[a] Some participants gave more than one reason. Percentages were based on total number of nonrandomized individuals per study center. Washington total does not include four participants who dropped out due to study center stopping randomization. California total does not include 21 participants who dropped out due to Safety and Endpoint Monitoring Committee stopping randomization.

effects. Physician support may buttress a participant's lagging interest.

Seven hundred twenty-three participants said they were unable to travel to the study center, did not show up at all, could not schedule a randomization visit within 6 months of the first visit, or were unable to be recontacted. This category of reason for dropping out appeared to be different between sites. The Seattle Study Center location in downtown Seattle had the highest percentage of participants who were unwilling to come to the study center. Providing a study center that is easy to travel to and has adequate parking would help.

Conclusions. Direct mail was an efficient method for recruiting high-risk smokers. We were able to contact a large number of individuals who would have been inaccessible via the usual methods of patient recruitment to clinical trials via physicians. The mail-in recruitment allowed successful screening of eligible individuals and self-screening because only those interested and motivated responded and entered the recruitment enrollment process. The 3-month placebo run-in also helped assure high retention in CARET; 89% of alive participants were still active after a mean of 4 years of follow-up, despite the release of the adverse findings from the ATBC trial.

This method can be exported readily to other sites in the United States and can be used by other trials using age as a primary eligibility criterion. With the cooperation of health insurers, this method can also provide a continuing source of age-eligible individuals because there is a constant flow of new individuals who join health plans, as well as individuals who age into the trial's age range criteria.

Because this method was based on health insurance subscribers, it was less successful in recruiting economically disadvantaged individuals, who are underrepresented among individuals with health insurance. This has also been a challenge in recruitment efforts of other prevention trials. Recruitment by direct mail of these populations would require mailing lists aimed at these specific populations, as well as more intensive community-based recruitment (14).

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