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BRIEF REPORT

Aspirin use and the incidence of breast, colon, ovarian, and pancreatic cancers in elderly women in the Iowa Women's Health Study

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Abstract
Purpose Few studies have evaluated the chemopreventive effect of aspirin on the cancer risk in elderly women. We examined associations between frequency, dose, and duration of aspirin use with incidence of 719 aspirin-sensitive cancers (cancers of colon, pancreas, breast, and ovaries) in the Iowa Women's Health Study (IWHS), a prospective cohort of women over 70 years old.
Methods Aspirin frequency, dose, and duration were self-reported in the 2004 IWHS questionnaire. Women were followed-up to 2011. Cancer cases were ascertained by linkage to the Iowa State Health Registry. Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95 % confidence intervals (CI).
Results Among the 14,386 women, 30 % were nonusers of aspirin; 34 % used low-dose aspirin, and 36 % used regular- or high-dose aspirin. Compared with nonuse of aspirin, the HRs (95 % CI) for incidence of aspirin-sensitive cancers were 0.87 (0.72–1.06) for regular to high doses of aspirin use, 0.95 (0.80–1.13) for aspirin use 6+ times per week, and 0.93 (0.74–1.17) for aspirin use for 10+ years. For cumulative aspirin use, HR (95 % CI) was 0.87 (0.70–1.09) for >60,000 mg of aspirin per year and 0.95 (0.75–1.21) for >280,000 mg of aspirin in their lifetime, versus nonuse of aspirin. Results were similar for the all-cause cancer death as an endpoint, with a significant inverse association observed between lifetime aspirin dose and cancer mortality [<95,000 mg vs nonuser HR 0.76 (0.61–0.95)].
Conclusions These findings suggest that aspirin use may prevent incident breast, colon, pancreatic, and ovarian cancer in elderly women.

Keywords Aspirin · NSAIDs · Elderly · Cohort · Cancer · Women

Introduction

In the USA, 53 % of cancers occur among individuals aged ≥65 years [1]. Eight percent of new cancers affect the oldest people (age 85+), a group expected to triple in size by 2040 [2, 3]. Overall, cancer incidence increases with age; rates generally peak and then decline between 75 and 90 years [4]. Cancer etiology and prevention in the elderly are relatively unexplored.

Both observational studies and randomized trials have found inverse associations between aspirin use and incidence of several site-specific cancers, as well as overall cancer incidence and mortality [5–15]. However, due to concerns about side effects, there have been limited general recommendations for widespread aspirin use for

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chemoprevention [13, 16]. Currently, the US Preventive Services Task Force is the only major American organization that has issued a broad recommendation to take aspirin to prevent a form of cancer, finding that the benefits of aspirin to prevent colorectal cancer outweighed the risks in adults aged 50–69; recommendations were less definitive for older adults aged 70–79, since the risk of harmful bleeding due to aspirin use increases with age [17]. Aspirin use and cancer prevention in the elderly are particularly relevant given that the US Preventive Services Task Force does not recommend mammography screening beyond age 74 years or routine colorectal screening over age 75 years [18, 19]. The incidence of these cancers is high at older ages, and thus, reducing incidence could lower treatment costs and associated comorbidities. US preventive services concluded that the "current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of cardiovascular disease and colorectal in adults aged 70 years or older" [17]. Therefore, more data on aspirin use in the elderly are needed, since older adults have not been included in aspirin trials and the risk–benefit profiles from trials in younger adults may not generalize to the elderly [20]. Additional data on the effective frequency, dose, and duration are also needed, particularly among elderly women [16, 21, 22].

The Iowa Women's Health Study (IWHS) is one of the few prospective, population-based studies to evaluate risk factors for incident cancers in a large sample of elderly women. The IWHS has collected data on aspirin frequency, duration, and dose and, thus, can address gaps about aspirin use and cancer outcomes in this population, which could be useful in informing risk–benefit decisions and cost-effectiveness analyses for recommended aspirin use in the elderly. In this IWHS analysis, we examined the patterns of aspirin use by elderly women (aged 73–87 years) and assessed whether or not aspirin use reduced the incidence of breast, colon, pancreatic, and ovarian cancers. We focused on these cancers because aspirin use was associated with the risk of these cancers in earlier studies in this cohort in the postmenopausal women aged 61–75 years [6–9, 11, 12, 28, 35], and in meta-analyses [5, 15, 16, 22, 27, 29–31].

Materials and methods

The rationale and design of the IWHS have been presented elsewhere [23]. In 1986, a questionnaire was distributed to 98,030 women aged 55–69 who had been randomly selected from the Iowa driver's license list. Those who completed a mailed questionnaire, 41,836 (42.7 %), were enrolled in the cohort. Five subsequent questionnaires were mailed for follow-up from 1986 to 2004, with high response rates. The questionnaires asked about lifestyle behaviors, sociodemographic factors, medical histories, and anthropomorphic measures. Age, height, level of education, and pack years of smoking were obtained at baseline, while smoking status, hormone replacement therapy (HRT) use, and diabetes were reported at baseline and at each follow-up. Weight, calcium use, multivitamin use, level of physical activity, and diet—via a food frequency questionnaire—were obtained from follow-up in 2004. Diet quality scores were calculated as the sum of adherence (0 = nonadherent, 0.5 = partially adherent, 1 = adherent) to the World Cancer Research Fund/American Institute for Cancer Research dietary recommendations for cancer prevention [24], which included six indicators: avoid high-sugar beverages; high fruit and vegetable intake, and dietary fiber intake; and limited consumption of red and processed meat, alcohol, and sodium [25].

The aim for this analysis, using data from 2004, was to characterize patterns of aspirin use in elderly women aged 73–87 years and examine associations with cancer incidence through 2011. The 2004 questionnaire included specific questions on the frequency, dose, and duration of use for aspirin (e.g., Bufferin, Anacin, and enteric-coated aspirin) and other NSAIDs (e.g., ibuprofen, Advil, Nuprin, and Motrin), and reasons for use and avoidance of these drugs. Both questions specifically directed respondents to exclude use of acetaminophen, Tylenol, prednisone, and cortisone. The categories for frequency of use for both questions were: (a) nonusers; and current users with a frequency of (b) less than once per week; (c) once per week; (d) 2–5 times per week; (e) 6–7 times per week; (f) 8–14 times per week; and (g) 15 or more times per week [7]. Categories for the number of years on each medication were (a) less than 1; (b) 1–4; (c) 5–9; (d) 10–19; (e) 20–39; and (f) 40 or more years. Possible doses of each medication were (a) low dose/children's/baby (81 mg); (b) regular (325 mg); and (c) extra strength (650 mg) for the aspirin product group and (a) regular or (b) extra strength for the other NSAIDs group.

To more fully capture and integrate information regarding aspirin usage patterns for these women, the individual measures of exposure levels of these drugs—dose, duration, and frequency—were combined to develop overall metrics to estimate aspirin use. An additional metric, "aspirin dose per year," was calculated as the product of dose (mg) with median frequency of aspirin use. The following medians were used for frequency of aspirin use based on the categories listed above: (a) 0; (b) 0.5; (c) 1; (d) 3.5; (e) 6.5; (f) 11; and (g) 15. Similarly, "lifetime aspirin dose" was the sum of "aspirin dose per year" for the duration of use: (a) 0.5; (b) 2.5; (c) 7; (d) 14.5; (e) 29.5; and (f) 40. Women who responded that they never

took aspirin were assigned an aspirin dose of "0" mg and a "0"-year duration. We conducted separate analyses using aspirin dose per year and lifetime aspirin dose (both were categorized into quartiles).

Cancer incidence among this cohort through 2011 was obtained by linking to the State Health Registry of Iowa, which is part of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program [1]. Cancer mortality through 2011 was ascertained through the National Death Index. Follow-up survey data indicated that the migration rate from Iowa among cohort members is <1 % annually, allowing nearly complete follow-up for cancer incidence [26]. The primary focus was incidence of cancers that were shown to have the strongest inverse association with aspirin use among younger women in this and other cohorts which included first primaries of breast [8, 11, 22, 27], colon [15, 21, 27, 28], ovarian [12, 29, 30], or pancreatic cancer [6, 31] (hereafter, called aspirin-sensitive cancers). In the additional analysis, we used underlying cause of death to study death from all cancers as the endpoint.

Of the 41,836 women in the IWHS cohort in 1986, we excluded from analysis 20,992 who either died ($n = 11{,}739$) before 2004, did not complete the 2004 questionnaire, or were lost to follow-up. Also excluded were women who had a cancer diagnosis other than nonmelanoma skin cancer at baseline ($n = 1{,}511$) or between baseline and 2005 ($n = 3{,}207$), were no longer living in Iowa in 2004 ($n = 1{,}295$), or whose response was inconsistent and thus deemed unreliable [aspirin frequency of use = never or left blank, but answered the dose or duration question ($n = 445$)]. This left 14,386 women with a total of 91,829 person-years of follow-up for analysis. This study was approved by the institutional review board.

Statistical analysis

Demographic characteristics were compared between groups using analysis of variance for continuous data and Chi-square tests for categorical data. Two nested Cox proportional hazard models were used to test the association between metrics of aspirin use and incident aspirin-sensitive cancers. Model 1 included only age (continuous) as an adjusting covariate. Model 2 included age, BMI (continuous), smoking (ever vs never), and frequency of nonaspirin NSAIDs use (nonuser, ≤1 time/week, 2–5 times/week, 6+ times/week). Women were treated as censored at date of last follow-up, death, or nonaspirin-sensitive cancer diagnosis, whichever occurred first. Parallel analyses compared categories of each aspirin metric (frequency, dose, and duration), aspirin dose per year, and lifetime aspirin dose.

Hazard ratios (HR) and confidence intervals (CI) were reported by level for the individual aspirin metrics and by quartile for the cumulative aspirin metrics. All p values were derived using Wald tests to assess trends across the hazard ratios. The proportional hazards assumption was assessed for each model using Chi-square tests and graphs derived from the scaled Schoenfeld residuals and found to hold for all models. Additional analyses separately stratified by history of heart disease and used the endpoint of death from any cancer. Using a Cox proportional hazard model with adjustment for age and a two-sided alpha level of 0.05, there was 80 % power to detect a true HR of 0.72 or less between the highest quartile of aspirin users and nonusers of aspirin.

A sensitivity analysis was conducted by restricting to consistent long-term users of aspirin based on a comparison of data from 1992, when frequency of aspirin use was first queried, and 2004. Additional sensitivity analyses were performed by excluding women who reported both using aspirin and reasons for avoiding aspirin in the 2004 data, as well as separately examining women with incident breast, pancreatic, or ovarian cancer and colon cancer. All analyses were performed using R 3.0.2 [32–34].

Results

Among the 14,386 women (mean age 78.6 years, range 73–87) in our analytical cohort, 4,180 (30 %) reported never using aspirin, 4,817 (34 %) reported using low-dose aspirin, and 5,083 (36 %) reported using regular- or high-dose aspirin. A total of 719 aspirin-sensitive cancer cases were identified, of which 394 were breast, 222 were colon, 54 were pancreatic, and 49 were ovarian cancers. Among these invasive cancers, the percentages with localized, regional, and distant stage of disease were 49, 24, and 14 %, respectively. Select patient characteristics are reported in Table 1. Low-dose aspirin users were substantially more likely to have a higher diet quality score and report multivitamin use, a higher level of physical activity, and a history of HRT use.

Among women who reported they did not use aspirin, the most common reason given for avoiding aspirin was because of other drugs taken (27 %), followed by unpleasant side effects (12 %), medical reasons (12 %), others (10 %), and religious or personal beliefs (1 %). Forty-four percent of nonusers did not give a reason for avoiding aspirin. Among women who did report taking aspirin, the most frequent reason for reported use was for heart issues, in the regular-/high-dose group and especially the low-dose group.

After multivariable adjustment (Model 2), there was an indication of an inverse association between all metrics of

Table 1 Participant characteristics by frequency of aspirin use, IWHS 2004

Patient characteristic	Aspirin dose[a]		
	Nonuser	Low dose	Regular/high dose
Prevalence of use[b], *n* (%)	4180 (30 %)	4817 (34 %)	5038 (36 %)
Age in 2004 (year)[c], mean (SD)	78.8 (4.0)	78.5 (3.9)	78.6 (4.0)
Obese (BMI $\geq$ 30 kg/m^2)[e], *n* (%)	706 (17 %)	744 (16 %)	872 (18 %)
Education[c], *n* (%)			
<HS	635 (15 %)	684 (14 %)	839 (17 %)
High school graduate	1777 (43 %)	2021 (42 %)	2147 (43 %)
Some college+	1765 (42 %)	2105 (44 %)	2041 (41 %)
Pack years of smoking[c], mean (SD)	6.2 (14.1)	6.6 (14.4)	6.5 (14.1)
History of smoking[cg], *n* (%)	1144 (28 %)	1346 (28 %)	1416 (29 %)
Calcium (mg)[b], mean (SD)	845 (476)	879 (494)	842 (494)
Diet quality score[b], mean (SD)	45.9 (10.3)	47.3 (10.3)	46.3 (9.9)
Diet quality score (tertiles)[b], *n* (%)			
$\leq$42	1367 (37 %)	1366 (32 %)	1540 (35 %)
(42,50]	1130 (31 %)	1349 (31 %)	1381 (31 %)
>50	1198 (32 %)	1623 (37 %)	1496 (34 %)
Multivitamin use[b], *n* (%)	2414 (60 %)	3229 (69 %)	2980 (61 %)
Level of physical activity[b], *n* (%)			
Low	2101 (51 %)	2026 (42 %)	2338 (47 %)
Medium	1094 (26 %)	1428 (30 %)	1464 (29 %)
High	969 (23 %)	1347 (28 %)	1226 (24 %)
History of HRT use[f], *n* (%)	1988 (48 %)	2525 (52 %)	2413 (48 %)
History of diabetes[f], *n* (%)	578 (14 %)	773 (16 %)	752 (15 %)
Reason for aspirin use[bd], *n* (%)			
Headaches	NA	209 (4 %)	1107 (22 %)
Body aches/pains, arthritis	NA	621 (13 %)	2246 (45 %)
Heart issues	NA	4172 (87 %)	2721 (54 %)
Other	NA	397 (8 %)	446 (9 %)
Avoid aspirin use[bd], *n* (%)			
Unpleasant side effects	515 (12 %)	NA	NA
Because of other drugs taken	1109 (27 %)	NA	NA
Medical reasons	480 (12 %)	NA	NA
Religious or personal beliefs	23 (1 %)	NA	NA
Other	409 (10 %)	NA	NA
Unknown	1821 (44 %)	NA	NA

HRT hormone replacement therapy

[a] Low dose = 81 mg; regular dose = 325 mg; high dose = 650 mg

[b] Reported in 2004

[c] Reported at baseline (1986)

[d] For these questions, participants were instructed to select all that apply

[e] Weight reported in 2004; height reported at baseline (1986)

[f] Reported up to 2004

[g] History of smoking: never versus current or former smoker

aspirin use and cancer incidence, although trends were statistically nonsignificant (Table 2). Compared with aspirin nonusers, the HRs of incident aspirin-sensitive cancer for women who reported using aspirin 6+ times per week, using aspirin for 10+ years, and using a regular to high dose of aspirin were 0.95 (95 % CI 0.80–1.13), 0.93 (95 % CI 0.74–1.17), and 0.87 (95 % CI 0.72–1.06), respectively (Table 2). Using the combined aspirin usage

Table 2 Age- and multivariable-adjusted associations between self-reported aspirin frequency, duration, and dose and incident aspirin-sensitive cancers, IWHS 2004–2011

Aspirin metric	No. of cancer cases	Model 1 HR (95 % CI)[a]	Model 2 HR (95 % CI)[b]
Dose			
Nonusers	209	1.00 (reference)	1.00 (reference)
Low dose[c]	257	1.03 (0.86–1.24)	1.01 (0.84–1.22)
Regular/high dose[c]	242	0.94 (0.78–1.13)	0.87 (0.72–1.06)
	Total: 708	$P_{trend} = 0.47$	$P_{trend} = 0.15$
Frequency			
Nonusers	209	1.00 (reference)	1.00 (reference)
≤1 time/week	88	0.92 (0.71–1.17)	0.87 (0.67–1.13)
2–5 times/week	71	0.99 (0.76–1.30)	0.94 (0.71–1.24)
≥6 times/week	344	0.99 (0.84–1.18)	0.95 (0.80–1.13)
	Total: 712	$P_{trend} = 0.91$	$P_{trend} = 0.71$
Duration			
Nonusers	209	1.00 (reference)	1.00 (reference)
<5 years	257	0.99 (0.82–1.18)	0.96 (0.80–1.16)
5–9 years	112	0.98 (0.78–1.23)	0.88 (0.69–1.12)
≥10 years	125	0.97 (0.78–1.21)	0.93 (0.74–1.17)
	Total: 703	$P_{trend} = 0.79$	$P_{trend} = 0.39$
Aspirin dose per year (quartiles)			
Nonuser	209	1.00 (reference)	1.00 (reference)
0 < 25,000 mg	121	0.99 (0.80–1.24)	0.94 (0.74–1.18)
25,001 < 60,000 mg	234	0.99 (0.82–1.20)	0.99 (0.81–1.19)
> 60,000 mg	144	0.96 (0.78–1.19)	0.87 (0.70–1.09)
	Total: 708	$P_{trend} = 0.75$	$P_{trend} = 0.35$
Lifetime aspirin dose (quartiles)			
Nonuser	209	1.00 (reference)	1.00 (reference)
0 < 95,000 mg	203	1.01 (0.83–1.22)	0.99 (0.81–1.20)
95,000 < 280,000 mg	131	1.00 (0.81–1.25)	0.95 (0.76–1.19)
> 280,000 mg	116	1.03 (0.82–1.30)	0.95 (0.75–1.21)
	Total: 659	$P_{trend} = 0.82$	$P_{trend} = 0.59$

Aspirin-sensitive cancers included breast, colon or rectal, ovarian, and pancreatic cancer

[a] Adjusted for age

[b] Adjusted for age, smoking, BMI, and nonaspirin NSAIDs use

[c] Low dose = 81 mg; regular dose = 325 mg; high dose = 650 mg

measures, compared to nonusers, the HRs of incident aspirin-sensitive cancer for women who took >60,000 mg of aspirin per year and >280,000 mg of aspirin in their lifetime were 0.87 (95 % CI 0.70–1.09) and 0.95 (95 % CI 0.75–1.21), respectively. The inverse association was stronger for breast, pancreatic, or ovarian cancer incidence; results were attenuated for colon cancer incidence (Supplemental Table 1). Results were similar after stratification by history of heart disease, with no evidence for effect modification (p values ranged from 0.10 to 0.48 for the various aspirin metrics in the multivariable analysis) (Supplemental Table 2).

After excluding women who reported both using aspirin and reasons for avoiding aspirin in the 2004 questionnaire ($n = 791$), HR estimates decreased in the group of women who used aspirin once per week or less (HR 0.79; 95 % CI 0.59–1.06). This suggests that the excluded women were infrequent users of low-dose aspirin for a short duration; indeed, 83 % of the women who were excluded and responded to all three individual aspirin metric questions reported using aspirin either <1/week, taking low-dose aspirin, or taking aspirin for <1 year. No appreciable changes were observed in risk estimates after excluding women who reported regular aspirin use (defined as 2 or more times/week) in 1992, but reported not using aspirin in 2004.

Importantly, results were consistent when using death from any type of cancer as an endpoint (Supplemental

Table 3), with HRs trending slightly lower than those for incident aspirin-sensitive cancers and a significant inverse association observed between lifetime aspirin dose and cancer mortality (<95,000 mg vs nonuser HR 0.76; 95 % CI 0.61–0.95).

Discussion

In our study, we observed an overall pattern of reduced risk of incident aspirin-sensitive cancers with intake of aspirin using various metrics of dose, duration, and frequency in elderly women over 7 years of follow-up. A protective effect was also shown for cancer mortality, with the strongest association observed using a cumulative lifetime dose aspirin metric.

Many studies, including previous studies in the IWHS cohort [6–8, 11, 35], have reported a benefit of aspirin use in middle-aged adults. Thus, with continued follow-up, more definitive evidence of inverse associations with cancer incidence may be seen in this study. The ability to detect an association between aspirin use and cancer was not an initial aim of the IWHS; thus, detailed information on aspirin usage patterns was only collected in 2004. Previous IWHS analyses, based on frequency of use, have reported inverse associations between frequent aspirin users (6+ times/week) and incident cancer of the breast (HR 0.72; 95 % CI 0.61–0.84), ovaries (HR 0.61; 95 % CI 0.37–0.99), pancreas (HR 0.40; 95 % CI 0.20–0.82), and colon (HR 0.76; 95 % CI 0.58–1.00) compared to nonusers; however, women in these studies were 61–75 years old at the start of follow-up, and aspirin dose and duration measures were not available from that questionnaire [7, 35].

The findings of a reduced risk of several types of cancer among middle-aged adult aspirin users are supported by several meta-analyses [15, 27, 29–31]. Frequent aspirin use (6+ times/week) was associated with reduced pancreatic cancer incidence (OR 0.57; 95 % CI 0.39–0.83) [31]. The meta-analysis of all cancer types by Bosetti et al. [27] reported reduced risks of both colorectal cancer and breast cancer for regular aspirin use vs nonuse of RR 0.73 (95 % CI 0.67–0.79) and RR 0.90 (95 % CI 0.85–0.95), respectively. However, results were heterogeneous across studies and included all ages; moreover, dose risk and duration risk were not clearly elucidated. In other meta-analyses, regular aspirin use, compared to nonregular use, was associated with a significantly reduced risk of invasive ovarian cancer (RR 0.88; 95 % CI 0.79–0.98) [30] and colorectal cancer (RR 0.81; 95 %CI 0.75–0.88) [15]. The meta-analysis by Algra et al. [22] included randomized studies; they found that the 20-year risk of death due to colorectal cancer was reduced in patients who used aspirin daily (OR 0.58; 95 % CI 0.44–0.78). However, due to the limited number of women enrolled in the randomized trials, estimates of the effect of aspirin use on cancers such as breast and ovarian could not be reliably obtained [22]. Although several meta-analyses included adults over 70 years of age as part of their analyses, none specifically investigated the associations in this older age group. Thus, to build evidence-based research data to inform policy on the use of aspirin in adults aged 70 years and older, additional studies of aspirin use, specifically, in this age group are needed [36].

As a relatively healthy 80-year-old woman has 8–10 years of remaining life [37], the high incidence rates of cancer during those years and the high cost of treatment underscore the need for research to identify preventive factors. The ongoing ASPREE trial will assess effects of aspirin use in adults aged ≥65 years, but results (for just a single dosage) will not be available until 2018 [38]. Importantly, the IWHS cohort is more representative of the overall population than clinical trials. Moreover, unlike numerous aspirin trials, IWHS was specifically designed to assess cancer incidence.

One of the limitations of this analysis was low power to detect small effects. We would have needed 13,234 events in our sample in order to achieve 80 % power to detect a hazard ratio of 0.95 such as we found between the highest quartile of lifetime aspirin dose and nonusers (Table 2). In this analysis, we aimed to evaluate whether or not there was a moderate to large effect of aspirin use on incident cancers; studies with larger sample sizes and longer follow-up time are needed to evaluate potential small to modest effects. The findings from our study can contribute to the future meta-analyses.

Another limitation is the potential selection bias in our cohort. The elderly women who responded to the 2004 survey tended to be healthier than nonresponders [39]. Therefore, it is possible that the women who were included in our study may benefit less from aspirin compared to the women who, for example, had systemic or other types of inflammation or cardiovascular disease by 2004 and did not respond to the survey.

In summary, this study indicates that aspirin use in elderly women may provide prophylactic benefit with respect to incident breast, colon, pancreatic, and ovarian cancers. These findings require confirmation in further research. In the future, participants in the IWHS cohort could be linked to outcomes in the Centers for Medicare and Medicaid Services (CMS) database that includes cardiovascular disease events and gastrointestinal bleeding, thus allowing for analyses of the potential benefits versus risks of aspirin use in this age group. To our knowledge, no other studies have evaluated aspirin use and incident cancer in elderly women over 70 years. Reducing cancer incidence with aspirin could lower costs and associated

comorbidities, which is particularly important in the elderly in the absence of screening and the underrepresentation in cancer trials of individuals 65 years of age or older [20]. Studying aspirin use in the prevention of colon, pancreatic, breast, and ovarian cancers is significant because inexpensive, safe strategies are needed to maintain health, enhance quality of life, and reduce medical interventions in the elderly.

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