Short Communication

Serum Dehydroepiandrosterone and Dehydroepiandrosterone Sulfate and the Subsequent Risk of Developing Colon Cancer[1]

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Abstract

This purpose of this study was to evaluate whether serum dehydroepiandrosterone (DHEA) and its sulfate conjugate, dehydroepiandrosterone sulfate (DHEAS), are associated with the likelihood of developing colon cancer. A nested case-control study was conducted using the serum bank and cancer registry in Washington County, Maryland. From a population of 20,305 county residents who donated blood in 1974, incident cases of colon cancer that occurred from 1975 to 1991 ($n = 117$) were matched to one cancer-free control by age, race, and sex. Serum specimens that were stored at −70°C since 1974 were assayed for DHEA and DHEAS. Compared with the controls, the mean serum concentrations of cases were 3% lower for DHEA ($P = 0.90$) and 13% lower for DHEAS ($P = 0.60$). When DHEA levels were analyzed according to fourths, no noteworthy associations were observed. Compared with the lowest fourth, the highest fourth of serum DHEAS was nonsignificantly associated with a halving in the risk of colon cancer (odds ratio, 0.50; 95% confidence limits, 0.18, 1.37; $P_{trend} = 0.22$), and further analyses showed the potential protective association was confined largely to males (highest-*versus*-lowest fourth odds ratio, 0.26; 95% confidence limits, 0.06, 1.16; $P_{trend} = 0.06$). This prospective study does not provide strong evidence that circulating DHEA and DHEAS concentrations are associated with the risk of colon cancer. Among men, DHEAS was associated with a decreased risk of colon cancer, but the association was within the bounds of chance. Further studies are needed to either support or refute the potentially promising lead hinted at by the results for DHEAS.

Received 11/10/98; revised 1/10/00; accepted 1/24/00.

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[1] Supported by research Grants CA 62988 from the National Cancer Institute and DAMD17-94-J-4265 from the Department of Defense. A. J. A. is a recipient of Preventive Oncology Academic Award CA73790 from the National Cancer Institute. G. W. C. is a recipient of Research Career Award HL21620 from the National Heart, Lung, and Blood Institute.

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Introduction

Colon cancer is the fourth most common cancer in the United States and the second highest cause of cancer mortality (1). The American Cancer Society estimates that during 1999, almost 95,000 persons will be diagnosed with colon cancer and that almost 48,000 people will die of the disease (1). One factor that can alter the risk of colon cancer is the hormonal milieu. For example, postmenopausal hormone replacement therapy reduces the risk of colon cancer among women (2). DHEA[3] and its sulfate conjugate, DHEAS, are steroids produced primarily by the adrenal gland. In humans, they circulate at high concentrations, but their specific physiological functions remain unknown, other than serving as precursors in the extra-adrenal synthesis of androgens and estrogens (3). They have properties, such as antioxidant capacity, inhibition of weight gain, and inhibition of cellular proliferation, that could enable them to protect against cancer (4, 5). Specifically, DHEA has been proposed as a potential protective agent against colorectal cancer (5). The results of animal studies provide some support for this hypothesis. The administration of DHEA to laboratory animals has been reported to inhibit tumor development in a number of anatomical sites (4). DHEA or DHEA analogues have been shown to reduce cancer incidence in various animal models of colon cancer, including the dimethylhydrazine model (6) and the rat azoxymethane model (7), but not all studies have demonstrated benefit (8). Because there is a lack of information concerning DHEA, DHEAS, and colon cancer among humans, we conducted a nested case-control study to investigate whether physiological concentrations of serum DHEA and DHEAS were associated with the risk of developing colon cancer.

Materials and Methods

Study Design. This study was carried out using the serum bank and cancer registry in Washington County, MD. The serum bank was established in 1974, when 20,305 community volunteers donated blood samples for use in research studies. After preparation of serum, the samples were stored at −70°C. Additional information was obtained from the study participants during a brief interview, when demographic and health-related information (*e.g.,* cigarette smoking history) were collected.

Among the cohort of blood donors, cases of colon cancer that occurred from January 1, 1975 through September 30, 1991 were ascertained by linkage to the Washington County cancer registry. This registry has been maintained by the staff of the Training Center for Public Health Research since 1968. Cancer cases are primarily ascertained from two sources: (*a*) discharge records from the Washington County Hospital; and (*b*) death certificates. A high proportion of cancer patients in the county

[3] The abbreviations used are: DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; OR, odds ratio; CL, confidence limit.

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receive their care at Washington County Hospital because it is the only general hospital in the county and has an excellent Oncology Service. As a branch of the Washington County Health Department, the Training Center for Public Health Research has access to death certificates. Linkage between the Washington County Cancer Registry and the Maryland State Cancer Registry showed that for 1993, the county registry ascertained 4% more cases of colon cancer than the state registry. The number of colon cancer cases expected on the basis of race/sex/age-specific rates from the Surveillance, Epidemiology, and End Results registries is similar to the number of observed cases in the cohort that donated blood for the serum bank, suggesting that reporting is essentially complete for this population.

Cases of rectal cancer were not included in the study. Of 121 incident cases of colon cancer that were diagnosed during this period and had no prior history of cancer (other than nonmelanoma skin cancer or cervical carcinoma *in situ*) that were used for a study of serum micronutrients (9), sufficient serum for the DHEA and DHEAS assays was available for 117 cases. One cancer-free control was matched to each case by age, sex, and race (all were white). The controls were age-matched to within 1 year of the case, except for three matched sets where the control was within 2 years of the case and one matched set where the control was 4 years older than the case.

Measurement of Serum DHEA and DHEAS. Aliquots of the stored serum specimens were prepared and were then immediately refrozen at −70°C until the assays were performed. DHEA and DHEAS were assayed using commercial RIA kits (Wien Laboratories, Succasunna, NJ) according to the manufacturer's instructions, except that hexane:methylene chloride (1:1) was used to extract the DHEA. These kits were selected based on a favorable comparison to reference methods used to measure DHEA and DHEAS (10). Matched case-control sets were assayed together in the same RIA run. The laboratory personnel were masked to the case-control status of the serum specimens. DHEAS has been observed to be stable at −20° for a storage period of similar duration (11).

Statistical Analysis. All data analyses accounted for the matched study design. The distributions of DHEA and DHEAS were skewed toward high values. Hence, the data were transformed by the natural logarithm for computing paired *t* tests to compare the mean concentrations of DHEA and DHEAS between the colon cancer cases and their matched controls. However, the means from the untransformed data are presented because they are easier to interpret and because similar inferences resulted from inspection of the transformed and untransformed results.

The quartiles of the DHEA and DHEAS distributions of the controls were used as the cutoff points to classify levels into fourths. Using the lowest fourth as the referent category, matched ORs and 95% CLs were estimated for each fourth via conditional logistic regression. The linear component of the trend in colon cancer risk according to serum steroid level was estimated using the likelihood ratio test from a conditional logistic regression model with a single quantitative variable coded with the exposure scores, which were the median of the controls' distribution for each fourth (12). The EGRET statistical software package was used for these analyses (SERC and Cytel, Seattle, WA).

To more fully describe the relationship between the steroids and colon cancer, further analyses were performed that specifically accounted for gender, anatomical site, hormone use, and cigarette smoking. Separate analyses were carried out for men and women because colon cancer mortality is higher in men than women and because men have higher circulating concentrations of DHEAS. The etiology of colon cancer may differ by anatomical site (13). Using a convention common to many epidemiological studies, colon cancer sites were grouped as right-sided (cecum, ascending colon, and transverse colon, which included the hepatic and splenic flexures) and left-sided (descending colon and sigmoid; Ref. 14). Hormone replacement therapy is associated with a decreased risk of colon cancer among women (2) and has also been observed to influence circulating concentrations of DHEA and DHEAS (15). Of the postmenopausal women in this study (55 cases and 54 controls), three cases and seven controls reported taking female hormones when they donated blood in 1974, which was accounted for by adjustment via multiple regression and separate analyses with hormone users excluded; these latter analyses were limited to postmenopausal women. Neither approach yielded results that altered the inferences from analyses that did not account for hormone use. Current cigarette smoking was considered as a potential confounder because cigarette smoking is associated with higher circulating levels of DHEA and DHEAS (16, 17). Adjustment of the associations between DHEA and DHEAS and colon cancer for cigarette smoking did not alter the overall tenor of the results presented.

Table 1 Percentage distribution of selected characteristics among colon cancer cases and matched controls at study baseline, Washington County, Maryland, 1974

	Cases (n = 117)	Controls (n = 117)
Sex		
Male	41.9	41.9
Female	58.1	58.1
Age (yr)		
≤44	8.5	8.5
45–54	30.8	30.8
55–64	35.0	35.0
65+	25.6	25.6
Cigarette smoking		
Never	44.4	53.0
Past	35.9	33.3
Current	19.7	13.7
Period diagnosed with cancer		
1975–1978	21.4	NA[a]
1979–1982	18.8	
1983–1986	33.3	
1987–1991	26.5	
Age diagnosed with cancer		
35–44	3.4	NA
45–54	9.4	
55–64	28.2	
65–74	26.5	
75+	32.5	
Cancer site		
Cecum and ascending	36.8	NA
Transverse colon	11.1	
Descending colon	10.3	
Sigmoid colon	36.8	
Other, multiple sites	5.1	

[a] NA, applies only to the case group.

Results

The colon cancer cases and the controls were matched by age and sex, but were also similar with respect to cigarette smoking, education, marital status, and the time between last meal and blood donation (Table 1). On average, the cases were

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Table 2 Mean serum DHEA and DHEAS concentrations among colon cancer cases and controls, Washington County, Maryland, 1974–1991

	DHEA (pmol/ml)				DHEAS (nmol/ml)			
	Cases	Controls	Percentage[a] difference	P^b	Cases	Controls	Percentage[a] difference	P^b
Total	6.7	6.9	−3	0.90	2.6	3.0	−13	0.60
Sex								
Male	6.1	6.7	−9	0.66	3.2	3.9	−18	0.27
Female	7.2	7.0	+3	0.65	2.2	2.3	−4	0.91
Colon site								
Right-sided	6.4	6.1	+5	0.29	2.7	3.0	−10	0.99
Cecum/ascending	6.2	6.3	−2	0.47	2.3	2.9	−21	0.62
Transverse	7.3	5.5	+33	0.35	4.0	3.4	+18	0.32
Left-sided	7.3	7.4	−1	0.71	2.4	2.9	−17	0.34
Descending	8.6	6.8	+26	0.60	3.1	3.0	+7	0.97
Sigmoid	6.9	7.6	−9	0.43	2.3	2.9	−21	0.27
Multiple/Other	5.0	9.4	−47	0.10	3.1	3.2	−3	0.76
Diagnosis date								
1975–1978	6.4	6.2	+3	0.59	2.4	2.6	−8	0.39
1979–1982	7.5	7.9	−5	0.77	2.8	3.4	−18	0.62
1983–1986	6.5	7.5	−13	0.45	2.8	3.2	−13	0.81
1987–1991	6.8	5.9	+15	0.12	2.4	2.7	−11	0.70

[a] Calculated as [(Case mean − Control mean)/Control mean] × 100.
[b] P from paired t test of log-transformed data.

Table 3 Relative odds of colon cancer according to fourths of serum DHEA and DHEAS concentrations, Washington County, Maryland, 1974–1991

	DHEA (pmol/ml)				DHEAS (nmol/ml)				
Cutoff points	No. of cases/controls	OR	95% CL	P_{trend}	Cutoff points	No. of cases/controls	OR	95% CL	P_{trend}
Total[a]									
≤3.73	31/30	1.0[b]			≤1.19	33/30	1.0[b]		
3.74–5.94	32/29	1.06	(0.50, 2.23)		1.20–2.43	29/29	0.81	(0.36, 1.82)	
5.95–9.58	29/29	0.94	(0.44, 2.04)		2.44–3.87	33/29	0.93	(0.45, 1.92)	
≥9.59	25/29	0.82	(0.37, 1.80)	0.54	≥3.88	22/29	0.50	(0.18, 1.37)	0.22
Males[c]									
≤3.86	11/13	1.0[b]			≤2.02	17/13	1.0[b]		
3.87–6.15	18/12	1.66	(0.50, 5.49)		2.03–3.16	14/12	0.81	(0.26, 2.56)	
6.16–8.93	7/12	0.77	(0.18, 3.28)		3.17–5.57	12/12	0.45	(0.12, 1.76)	
≥8.94	13/12	1.32	(0.33, 5.36)	0.97	≥5.58	6/12	0.26	(0.06, 1.16)	0.06
Females[d]									
≤3.71	20/17	1.0[b]			≤0.95	16/17	1.0[b]		
3.72–5.82	15/17	0.71	(0.25, 2.04)		0.96–1.54	17/17	1.06	(0.43, 2.57)	
5.83–9.68	15/17	0.76	(0.31, 1.90)		1.55–3.18	18/17	1.15	(0.41, 3.18)	
≥9.69	18/17	0.88	(0.33, 2.33)	0.94	≥3.19	17/17	1.07	(0.39, 2.91)	0.89

[a] $n = 117$ matched sets.
[b] Referent category.
[c] $n = 49$ matched sets.
[d] $n = 68$ matched sets.

diagnosed with colon cancer 9 years after donating blood. As expected, the majority of these individuals were diagnosed with tumors of either the cecum/ascending colon or the sigmoid colon. The percentage of right-sided colon cancer was similar among men (55%) and women (47%). Serum concentrations of DHEA and DHEAS were significantly correlated among the controls ($r = 0.65$; $P < 0.001$).

The colon cancer cases and the controls had similar mean serum concentrations of DHEA (Table 2). Serum DHEAS concentrations were 13% lower among the cases than the controls. The case-control percentage difference in mean DHEAS levels was slightly more pronounced among men (−18%) than women (−4%). When analyzed according to tumor location, cases had serum DHEAS levels that were 21% lower than controls if their tumors occurred in the cecum ($P = 0.62$) or sigmoid colon ($P = 0.27$). In analyses stratified according to when the case was diagnosed, cases had serum levels of DHEAS that were from 8 to 18% lower throughout the follow-up interval. None of the case-control differences in mean serum DHEAS concentrations were statistically significant.

When analyzed according to fourths, DHEA was not associated with the risk of colon cancer (Table 3). For DHEAS, the highest-*versus*-lowest fourth was associated with a halving in the risk of colon cancer, but neither this association nor the test for trend was statistically significant. When the data were analyzed separately for men and women, the only notable association was a trend of borderline statistical significance among men ($P = 0.06$), suggesting that for each incremental increase in fourth of serum DHEAS concentration, the risk of colon cancer decreased by approximately one-fourth. Formal tests for interaction in these associations by gender were not

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Table 4 Relative odds of colon cancer by anatomic subsite according to fourths of serum DHEA and DHEAS concentrations, Washington County, Maryland, 1974–1991

DHEA (pmol/ml)					DHEAS (nmol/ml)				
Cutoff points	No. of cases/controls	OR	95% CL	P_{trend}	Cutoff points	No. of cases/controls	OR	95% CL	P_{trend}
Right-sided[a]									
≤2.65	7/14	1.0[b]			≤1.19	14/14	1.0[b]		
2.66–5.46	24/14	4.46	(1.11, 17.87)		1.20–2.54	17/14	1.07	(0.38, 3.06)	
5.47–7.16	9/14	1.81	(0.40, 8.25)		2.55–4.53	16/14	1.00	(0.34, 2.94)	
≥7.17	16/14	2.98	(0.72, 12.40)	0.58	≥4.54	9/14	0.52	(0.13, 2.05)	0.27
Left-sided[c]									
≤3.91	16/14	1.0[b]			≤1.14	15/14	1.0[b]		
3.92–7.42	13/14	0.80	(0.28, 2.25)		1.15–2.23	13/14	0.72	(0.21, 2.50)	
7.43–9.76	12/14	0.72	(0.23, 2.28)		2.24–3.77	19/14	1.07	(0.36, 3.22)	
≥9.77	14/13	0.91	(0.27, 3.04)	0.94	≥3.78	8/13	0.34	(0.07, 1.75)	0.22

[a] Cecum, ascending colon, and transverse colon ($n = 56$ matched sets).
[b] Referent category.
[c] Descending colon and sigmoid ($n = 55$ matched sets).

statistically significant ($P = 0.42$ for DHEA and $P = 0.66$ for DHEAS).

The results of analyses stratified by right- and left-sided colon cancer are summarized in Table 4. Serum DHEA above the lowest fourth was associated with increased risk of right-sided colon cancer, with no evidence of a monotonic trend. For left-sided tumors, no trends were present, but the OR for the lowest fourth of serum DHEAS was in the protective direction. The results of site-specific analyses for cases with tumors located in the cecum/ascending colon ($n = 43$ matched sets) or sigmoid colon ($n = 43$ matched sets) mirrored the results observed for the broader groupings (data not shown), with the observations noted above simply being slightly more pronounced in the more refined anatomical categories.

A source of potential concern was that the cases who were diagnosed with colon cancer shortly after they donated blood may have had their circulating DHEA and DHEAS levels altered by the presence of preclinical disease. To account for this possibility, analyses were conducted that were limited to the cases diagnosed with colon cancer 5 or more years after the blood was collected ($n = 92$ matched sets). The results of these analyses were essentially the same as the results for the entire study population (data not shown). Neither time from blood collection to diagnosis ($P > 0.30$ for both steroids) nor cases' ages of diagnoses ($P > 0.50$ for both steroids) were observed to significantly modify the associations between DHEA or DHEAS and colon cancer.

Discussion

The results of animal studies suggest that DHEA may protect against cancer of the colon. We conducted a nested case-control study to evaluate whether circulating concentrations of DHEA and DHEAS influence the risk of developing colon cancer. Overall, DHEA was not associated with colon cancer risk. Although the results did not provide strong support of an association between DHEAS and colon cancer, the relative risk estimates for the highest serum concentrations tended to be in the protective direction. Compared with the lowest fourth, the highest fourth of serum DHEAS was associated with a halving in the risk of colon cancer.

The protective association observed for DHEAS was largely confined to men. Among men, the risk of colon cancer was reduced by approximately one-fourth per increase in fourth of serum DHEAS, but even this trend was not statistically significant. The results of such subgroup analyses need to be interpreted cautiously because when many comparisons are made, the likelihood increases that an association will be observed simply because of the play of chance. The different association between DHEAS and colon cancer by gender does not appear to be explained by the tumor site within the colon, because the distribution of tumors by anatomical site was similar for men and women. A tenable explanation for why DHEAS, but not DHEA, would be protective is not readily apparent but could relate to factors such as DHEAS supplying a larger reservoir of precursor hormone or the extent that DHEAS is converted to DHEA playing a role. Because endogenous hormone levels represent a ubiquitous exposure, the observed associations would also be more convincing if they were in accord with the sex-specific population patterns of colon cancer, but they are not: the age-adjusted incidence of colon cancer is higher among men than women (18). This argument is counterbalanced by the fact that the sex-specific patterns of colon cancer incidence reflect the complex interplay between all risk and protective factors, so that differential protection by one factor such as DHEAS could conceivably be offset by greater risk from other factors among males. Furthermore, the results from animal studies do not rule out the possibility that a protective association could exist for DHEAS and not DHEA, because male F344 rats with DHEA-supplemented diets experienced even larger increases in serum DHEAS than DHEA (8). The possibility of a protective association for DHEAS among males is also intriguing because DHEAS circulates at higher concentrations among men than women (11, 19–21), lending some support to the notion that this association may be biologically relevant. Consistent with previous reports, men had higher DHEAS concentrations than the women in this study; the mean serum DHEAS concentration among the male controls was 67% higher than among the female controls (Table 2; $P = 0.0005$).

A strength of this study is that it was prospective, with a follow-up interval that ranged up to 17 years and averaged 9 years. The long period of follow-up confers the additional advantage that the serum specimens were collected in an era before DHEA supplementation was available, an issue of concern for studies that are currently under way. The presence of preclinical disease was not likely to have affected the results, because the results were not materially altered when the cases of colon cancer diagnosed in the 5-year period immediately after blood donation were excluded from the analyses. Of principal importance in the design of this study was that age

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was carefully controlled for, with almost all of the controls matched to within 1 year of the case's age. This is crucial because DHEA and DHEAS decrease gradually throughout adulthood (11, 17, 20, 22, 23), and the risk of colon cancer increases with age, so that failure to carefully account for age could give rise to spurious results.

However, the study also has limitations which should be considered when interpreting the results. A larger study would have greater statistical power to detect associations of the magnitude observed in the present study, and this issue is particularly relevant to the present study for subgroup analyses, where strata sizes were often small. DHEAS concentrations are relatively stable throughout the day, but diurnal variation has been observed for DHEA (24–30). The collection of blood samples in the present study was confined to daytime hours, limiting the impact that diurnal variation may have had on the study findings. Nevertheless, it is possible that the evidence favoring an association with DHEAS, but not DHEA, with colon cancer could at least partly be attributable to the greater stability of DHEAS throughout the day, reducing the extent of measurement error. In addition, the study would be strengthened if we were able to account for several known risk factors for colon cancer when assessing the association between serum DHEA and DHEAS concentrations and colon cancer; these include factors such as family history, alcohol drinking, dietary intake, body mass index, and physical activity. Future studies that account for a broader range of colon cancer risk factors will help to discern whether confounding may at least partly explain the pattern of associations observed in the present study.

The results of this prospective serological study thus do not provide strong evidence that circulating concentrations of DHEA and DHEAS influence the risk of colon cancer. The results for DHEAS, particularly among males, were compatible with a protective association but were within the bounds of chance. Given the potential value of identifying nonhereditary factors that influence the risk of colon cancer, the magnitude of the inverse association observed in the present study, especially among males, offers a lead for further studies to assess whether this observation indeed holds relevance to colon cancer.

Acknowledgments

We gratefully acknowledge the comments of anonymous reviewers to an earlier version of the manuscript.

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