Re: A Case–Control Study of Levothyroxine and the Risk of Colorectal Cancer

Responding to the study of Rennert et al. (1), we analyzed levothyroxine in relation to risk of colorectal cancer in the context of our screening of pharmaceuticals for possible carcinogenesis (2) in the Kaiser Permanente Medical Care Program in

Table 1. Risk of colon and rectal cancer in relation to previous use of levothyroxine*

Sex and tumor site	Levothyroxine use		*P*†	0 levothyroxine prescriptions; No. of case patients/control subjects‡
	OR (95% CI); No. of case patients/control subjects	OR (95% CI); No. of case patients/control subjects		
	<5 y	≥5 y		
Men				
Colon	1.03 (0.90 to 1.18); 230/11 062	0.87 (0.71 to 1.07); 99/5620	.18	Referent; 5747/286 010
Rectum	0.82 (0.64 to 1.04); 70/4207	0.66 (0.45 to 0.97); 28/2058	.03	Referent; 2698/133 217
All women				
Colon	0.98 (0.90 to 1.07); 586/29 542	0.90 (0.81 to 1.01); 381/20 759	.06	Referent; 5164/255 303
Rectum	0.89 (0.76 to 1.06); 162/8907	0.97 (0.78 to 1.19); 102/5220	.74	Referent; 1669/82 316
Women >55 y§	None/< 5y§	≥5 y		
No HT				
Colon	Referent; 3009/139 769	0.88 (0.75 to 1.04); 165/8469	.14	
Rectum	Referent; 793/36 652	1.05 (0.75 to 1.47); 41/1801	.77	
On HT				
Colon	Referent; 1106/62 610	0.86 (0.71 to 1.04); 130/8395	.12	
Rectum	Referent; 268/16 525	1.35 (0.94 to 1.93); 42/1876	.11	

* CI = confidence interval; HT = hormone therapy; OR = odds ratio. All statistical tests were two-sided.

† ≥ 5 years vs referent.

‡ Referent group.

§ For the analysis of women older than 55 years by HT use, nonusers of levothyroxine were combined with those who took levothyroxine for 5 years or less, to be consistent with Rennert et al. (1).

northern California (KPNC), a comprehensive prepaid health-care system. Rennert et al. (1) found that use of levothyroxine for at least 5 years was associated with a reduced risk in all subjects and that among postmenopausal women, risk was lower among nonusers of hormone therapy (HT) than among users.

We performed case–control analyses of colon and rectal/rectosigmoid cancer separately using conditional logistic regression and two-sided statistical tests. The study period was August 1994 through February 2008, and the source cohort was over 90% of KPNC subscribers with at least partial coverage of payment for prescriptions. Cancer case patients (colon: N = 12 207; rectum/rectosigmoid: N = 4729) were identified in the Kaiser Permanente Cancer Registry, a contributor to the Surveillance, Epidemiology, and End Results (SEER) program (http://www.seer.cancer.gov), and prescription dispensing records were obtained from all KPNC outpatient pharmacies. For each case patient, we selected up to 50 risk set control subjects, matched for age, sex, year of cohort entry, and duration of follow-up (colon: N = 608 296; rectum/rectosigmoid: N = 235 925). We duplicated the 5 or more years duration-of-use breakpoint of Rennert et al. (1) but also subdivided the remaining subjects into no use and use of less than 5 years, except when comparing HT users and nonusers. Duration of use was calculated by summing the days' supply of each prescription dispensed. Lacking menopausal status, we assumed that women older than 55 years were postmenopausal. Use of HT was defined as at least two dispensed prescriptions at any time during the study period before diagnosis or index date. Data on risk factors other than age and sex for colorectal cancer were not readily available, but control for some of these by Rennert et al. (1) made virtually no difference in their main finding.

Risk of rectal cancer was more than 30% lower in men who used levothyroxine for at least 5 years, relative to the referent group (Table 1). Risk for colon cancer appeared to be slightly reduced, but this finding was not statistically significant. In women, risk for cancer at both sites appeared slightly reduced, but statistical significance was at best borderline. Among women older than 55 years, risk of colon cancer was virtually the same for users and nonusers of HT. Risk of rectal cancer showed non-statistically significant increases in both groups but was less marked in nonusers of HT.

Our findings provide support for a reduction in risk of rectal cancer in men associated with long-term use of levothyroxine. Men who were long-term users were also at lower risk for colon cancer, but the association was weaker and not statistically significant. In women, the associations for both sites were negative and weak with at best borderline statistical significance. The negative associations were not more pronounced among women of menopausal age not on HT.

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References

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