VOLUME 27 · NUMBER 27 · SEPTEMBER 20 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Use of Hormone Replacement Therapy and the Risk of Colorectal Cancer

Gad Rennert, Hedy S. Rennert, Mila Pinchev, Ofer Lavie, and Stephen B. Gruber

From Department of Community Medicine and Epidemiology, Carmel Medical Center; Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology; Clalit Health Services National Cancer Control Center; Gyneco-oncology Unit, Department of Obstetrics and Gynecology, Carmel Medical Center, Haifa, Israel; and Departments of Epidemiology, Internal Medicine, and Human Genetics, University of Michigan, Ann Arbor, MI.

Submitted January 18, 2009; accepted May 12, 2009; published online ahead of print at www.jco.org on August 24, 2009.

Supported by Grant No. 1R01CA81488 from the National Cancer Institute.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Gad Rennert, MD, PhD, Department of Community Medicine and Epidemiology, Carmel Medical Center, 7 Michal St, Haifa 34362, Israel; e-mail: rennert@tx.technion.ac.il.

0732-183X/09/2727-4542/$20.00

DOI: 10.1200/JCO.2009.22.0764

ABSTRACT

Purpose
Estrogen/progestin replacement therapy is prescribed to women in menopause for purposes of postmenopausal symptom control or prevention of hormone deficiency–related diseases such as osteoporosis. Such treatments have formerly been shown to be associated with lower colorectal cancer risk in an as yet unknown mechanism.

Patients and Methods
The Molecular Epidemiology of Colorectal Cancer study was a population-based case-control study in northern Israel of patients with colorectal cancer who were diagnosed between 1998 and 2006, and age-, sex-, clinic-, and ethnicity-matched population controls. Use of hormone replacement therapy (HRT) was assessed using a structured interview and validated by studying prescription records in a subset of patients for whom they were available.

Results
Two thousand four hundred sixty peri/postmenopausal women were studied from among 2,648 patients with colorectal cancer and 2,566 controls. The self-reported use of HRT was associated with a significantly reduced relative risk of colorectal cancer (odds ratio [OR], 0.67; 95% CI, 0.51 to 0.89). This association remained significant after adjustment for age, sex, use of aspirin and statins, sports activity, family history of colorectal cancer, ethnic group, and level of vegetable consumption (OR, 0.37; 95% CI, 0.22 to 0.62). Statistically significant interactions were seen between use of HRT and use of aspirin and involvement in sports activity. Using pharmacy data, only users of combined oral preparations demonstrated a significant negative association with colorectal cancer.

Conclusion
The use of oral HRT was associated with a 63% relative reduction in the risk of colorectal cancer in postmenopausal women after adjustment for other known risk factors. This effect was not found in aspirin users and women with intensive sports participation.

J Clin Oncol 27:4542-4547. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the United States, with approximately 153,760 new cases and 52,180 deaths projected for 2007.[1] Hormone replacement therapy (HRT) was reported to be associated with reduced risk of CRC.[2-11] Yet, the mechanism of this protective effect is still unclear. Previous studies have suggested that the negative association between the use of HRT and CRC is more marked in current users[4,11-13] and longer-term users,[14] stronger in older women,[2] and in women with lower body mass index (BMI).[2,9,13] The effects of HRT could differ by type of medication.[4,5,15] It was also suggested that history of HRT use is associated with lower mortality from CRC[11,16] and lower rate of colonic adenomas.[13,14] We evaluated data collected in a large population-based study for associations between the use of HRT and the occurrence of CRC.

PATIENTS AND METHODS

Participants

The Molecular Epidemiology of Colorectal Cancer study was a population-based case-control study of incident CRC in northern Israel. Patients were eligible for participation if they were diagnosed with CRC between March 31, 1998, and March 31, 2006, and lived in a geographically defined area of northern Israel. Controls were identified from the same source population with the use of the Clalit Health Services (CHS) database. CHS is the largest health care provider in Israel and covered, during the study years, approximately 70% of the older population (persons at least 60 years of age). Health care coverage in Israel is mandatory and is provided by four groups akin to non-for-profit health maintenance organizations

(HMOs). Thus, all study participants (patients and controls) had similar basic health insurance plan and similar access to health services. Controls were individually matched to patients according to the year of birth, sex, residence as defined by primary clinic location, and ethnic group (Jewish *v* non-Jewish). Potential controls were excluded if they had a history of CRC. Participants provided written informed consent at the time of enrollment and were interviewed to obtain information about their personal and family history of cancer, reproductive history, medical history, medication use, and health habits including a dietary questionnaire as formerly described.[17] Diagnoses of CRC were made independently by the diagnosing hospitals and were confirmed by means of a standardized pathologic review by one pathologist. The institutional review boards at the Carmel Medical Center (Haifa, Israel) and the University of Michigan (Ann Arbor, MI) approved all procedures.

Exposure Data

The use of HRT was determined on the basis of a self-report by study participants who were asked specifically about ever use of hormones. Women were asked to define their menopause status at time of diagnosis. Women who did not respond to this question were assigned a postmenopausal status if they were older than 55 years. For the purpose of this analysis, we included all reported uses of hormones after age 45. We further evaluated the use of hormones from a pharmacy file that was available for study participants belonging to the largest HMO-type organization in Israel (Clalit Health Services). From this file, we also extracted information on type of hormone used and duration of use. Analyses using these data were again restricted only to usage after the age of 45 years. Hormones included in the analysis were estrogen only preparations and combined estrogen-progestin preparations either in the form of oral pills or patches. All creams and gels as well as vaginal tablets and progestin-only preparations were excluded. The use of statins for 5 years or longer, with type and dose, was recorded from the questionnaire. The use of aspirin and other nonsteriodal anti-inflamatory drugs (NSAIDs) was recorded in more detail and included dose and duration of use, as was the use of female HRT. For analyses of aspirin, exposure was defined as at least 3 years of daily use, as the effects were not different from those of 5-year users, while this choice offered more power for multivariate models. The report of colon or rectal cancer in at least one first-degree relative was considered to represent a family history of CRC. Assessment of physical activity was based on a validated instrument.[18] Sports activity was the dimension considered in our analyses since it was most strongly associated with CRC risk in our data. Ethnic group was determined by assessing participants' religious affiliation, self-described ethnic group, and the country of birth of their parents and grandparents. A validated food-frequency questionnaire adapted to the Israeli diet[19] was used to study the association of various dietary components with the risk of CRC.[20] Vegetable consumption was categorized into two groups based on the median number of servings consumed per day in the control group (fewer than 5, and 5 or more servings per day). The lower category of consumption was used as the reference category. CRC screening in Israel was uncommon during most of the study period and therefore screening behavior was found not to be a significant variable.

Validation of HRT Use

We matched self-reports of use of HRT against the prescription records of CHS enrollees to verify usage. Prescription records were available since 1998 and include the number of prescriptions filled per year. We therefore sought prescription records for HRT preceding diagnosis in cases and preceding enrollment in the study for controls. For purposes of internal validation, results are presented for self-reported HRT use, pharmacy record–based HRT use, and for a combined data set from both sources.

Statistical Analysis

Statistical analyses were performed with the use of SPSS software, version 15.0 (SPSS Institute, Chicago, IL) with reported two-sided *P* values. A contingency table was used to assess crude associations between HRT use and the risk of CRC. To account for the study design, matched analyses were performed with the use of both contingency-table methods and conditional logistic regression and estimates stemming from unconditional logistic regression models were used if no differences in results were found between the conditional and unconditional model. These techniques were used to assess the main association between HRT use and the risk of CRC, to adjust for confounding, and to identify potential effect modification.

RESULTS

A total of 230 women older than 45 years (10.6%) reported ever using HRT among the 2,460 female patients and controls in our study (of whom 2,169 had HRT use data), representing 8.7% of the patients and

Table 1. Comparison of Major Study Variables Between Patients and Controls: MECC Study

	Unpaired					Paired				
	Patients		Controls			Patients		Controls		
Variable	No.	%*	No.	%*	*P* for Difference	No.	%*	No.	%*	*P* for Difference
No. of participants	1,234		1,226			1,195		1,195		
Mean age, years	70.0		70.6		NS	69.9		70.6		NS
Ethnicity					NS					NS
Non-Jewish	154	12.5	141	11.5		152	12.7	138	11.5	
Jewish	1,080	87.5	1,085	88.5	< .001	1,043	87.3	1,057	88.6	< .001
Ashkenazi	846	68.6	777	63.4		816	68.3	755	63.2	
Sephardi	207	16.8	290	23.7		201	16.8	285	23.8	
Mixed	27	2.2	18	1.5		26	2.2	17	1.4	
Family history of CRC, first degree	156	13.2	104	8.7	< .001	153	13.4	102	8.7	< .001
Sports activity	303	25.2	470	38.4	< .001	296	25.4	460	38.6	< .001
Vegetables, ≥ 5/d	634	54.7	718	58.9	.043	612	54.6	706	59.4	.02
Aspirin use, daily, 3+ years	134	11.1	231	18.9	< .001	129	11.1	222	18.7	< .001
Statins use, 5+ years	75	6.2	137	12.0	< .001	74	6.4	133	12.0	< .001
HRT use (ever) self-report	89	8.7	141	12.3	.003	88	8.8	140	12.6	.005
BMI > 30 (obese)	287	27.7	324	29.0	NS	279	27.8	318	29.1	NS

Abbreviations: MECC, Molecular Epidemiology of Colorectal Cancer; NS, not significant; CRC, colorectal cancer; HRT, hormone replacement therapy; BMI, body mass index.
*Because of missing data, some percentages were calculated from differing denominators.

12.3% of the controls. Self-reported HRT use was confirmed in 135 (63.1%) of 214 users whose pharmacy records were available. In this pharmacy database, 287 of the study participants were identified as hormone users (12.9% of all HMO female insurees enrolled in the study). Table 1 describes the distribution of self-reported HRT use and other risk-related variables in the study participants.

Univariate Analysis

The reported use of HRT was associated with an overall CRC risk-reduction of 33% (odds ratio [OR], 0.67; 95% CI, 0.51 to 0.89).

Similar effects were seen when data from the pharmacy records were analyzed (OR, 0.70; 95% CI, 0.54 to 0.90; n = 287 users) and when data were combined from both self-reported and pharmacy records (OR, 0.67; 95% CI, 0.53 to 0.85; n = 366 users).

When evaluating the association between the use of HRT and other known risk or protective factors for CRC, similar associations were found between women with and without family history, females with high and low consumption of vegetables, women with normal weight and obese women, and users and nonusers of statins (Table 2). However, the associations were significantly stronger in sedentary women and a clear interaction was found with the use of aspirin, where a strong negative association between HRT and CRC risk was noted only among nonaspirin users who used HRT (Table 3).

From the pharmacy records it can be seen that the negative association was seen mostly in past users and not in current or recent (last 2 years) users (OR, 0.50; 95% CI, 0.33 to 0.75; OR, 0.85; 95% CI, 0.62 to 1.17, respectively). The effect was seen in users of combined estrogen-progestin preparations (n = 151; OR, 0.71; 95% CI, 0.50 to 0.99) and did not reach statistical significance in users of estrogen only preparations (n = 78; OR, 0.81; 95% CI, 0.51 to 1.29). Also, while the effect was strong with oral preparations (n = 239; OR, 0.68; 95% CI, 0.52 to 0.90) it was not seen among users of transdermal patches (n = 26; OR, 1.00; 95% CI, 0.46 to 2.18).

A similar distribution of tumor sites, tumor stage, and tumor grade were found in self-reported HRT users and HRT nonusers

Table 3. Self-Reported HRT, Use of Aspirin, and Risk of Colorectal Cancer in Postmenopausal Women

Variable	Patients No.	Patients %	Controls No.	Controls %	Odds Ratio	95% CI
All postmenopausal						
HRT use	88	8.7	141	12.3	**0.67**	**0.51 to 0.89**
No HRT use	926	91.3	1,001	87.7		
Aspirin nonusers						
HRT use	76	8.5	127	13.9	**0.58**	**0.43 to 0.78**
No HRT use	813	91.5	787	86.1		
Aspirin users						
HRT use	12	9.6	14	6.1	1.62	0.73 to 3.63
No HRT use	113	90.4	214	93.9		
All postmenopausal						
Aspirin use	125	12.3	228	20.0	**0.56**	**0.45 to 0.71**
No aspirin use	889	87.7	914	80.0		
HRT nonusers						
Aspirin use	113	12.2	214	21.4	**0.51**	**0.40 to 0.66**
No aspirin use	813	87.8	787	78.6		
HRT users						
Aspirin use	12	13.6	14	9.9	1.43	0.63 to 3.26
No aspirin use	76	86.4	127	90.1		
Interaction term HRT × aspirin					**2.80***	**1.19 to 6.61**

NOTE. Bold font indicates statistical significance.
Abbreviation: HRT, hormone replacement therapy.
*P = **.019.**

Table 2. Univariate Effects of HRT Use and Risk of Colorectal Cancer, for Postmenopausal Women: MECC Study

Variable	Based on HRT Data From: Questionnaire Odds Ratio	Questionnaire 95% CI	Pharmacy Records Odds Ratio	Pharmacy Records 95% CI	Both Sources Odds Ratio	Both Sources 95% CI
Sports, yes	1.06	0.71 to 1.57	1.16	0.79 to 1.70	1.00	0.71 to 1.43
No	**0.59**	**0.39 to 0.90**	**0.55**	**0.39 to 0.79**	**0.61**	**0.44 to 0.84**
Vegetables, 5+	**0.66**	**0.46 to 0.95**	0.86	0.63 to 1.18	**0.74**	**0.55 to 0.99**
< 5	0.73	0.46 to 1.17	**0.49**	**0.31 to 0.79**	**0.60**	**0.40 to 0.90**
BMI						
Normal	**0.50**	**0.30 to 0.84**	0.66	0.42 to 1.02	**0.64**	**0.43 to 0.96**
Overweight	0.90	0.59 to 1.37	0.81	0.53 to 1.23	0.84	0.58 to 1.23
Obese	0.66	0.36 to 1.23	0.65	0.37 to 1.14	**0.56**	**0.33 to 0.94**
Statins, yes	0.54	0.17 to 1.72	0.32	0.07 to 1.48	0.44	0.16 to 1.23
No	**0.67**	**0.50 to 0.90**	**0.71**	**0.54 to 0.93**	**0.68**	**0.53 to 0.87**
Aspirin, yes	1.62	0.73 to 3.63	0.89	0.39 to 2.02	1.30	0.68 to 2.49
No	**0.58**	**0.43 to 0.78**	**0.64**	**0.49 to 0.84**	**0.59**	**0.46 to 0.76**
FH, yes	0.70	0.33 to 1.52	0.47	0.22 to 1.01	0.58	0.29 to 1.15
No	**0.64**	**0.47 to 0.87**	**0.71**	**0.54 to 0.93**	**0.67**	**0.52 to 0.86**
Aspirin × HRT	**2.80**	**1.19 to 6.61**	1.37	0.58 to 3.26	**2.18**	**1.08 to 4.38**
P	**.019**		.457		**.027**	
Sports × HRT	**1.79**	**1.01 to 3.18**	**2.06**	**1.22 to 3.47**	**1.63**	**1.01 to 2.63**
P	**.046**		**.007**		**.044**	

NOTE. Bold font indicates statistical significance.
Abbreviations: MECC, Molecular Epidemiology of Colorectal Cancer; HRT, hormone replacement therapy; BMI, body mass index; FH, family history.

Table 4. Tumor Characteristics in Users and Nonusers of HRT for Postmenopausal Women: MECC Study

Characteristic	Self-Reported HRT Users		No Reported Use of HRT		*P* for Difference	Pharmacy-Based HRT Users		No Pharmacy Records of HRT Use		*P* for Difference
	No.	%	No.	%		No.	%	No.	%	
Site of cancer					NS					NS
Colon	62	78.5	653	77.5		75	77.3	628	77.9	
Right	27	34.2	337	40.0		35	36.1	334	41.4	
Left	35	44.3	316	37.5		40	41.2	294	36.5	
Rectum	17	21.5	190	22.5		22	22.7	178	22.1	
Stage					NS					NS
1, 2	48	59.3	508	59.4		60	63.2	482	58.4	
3, 4	33	40.7	347	40.6		35	36.8	344	41.6	
Grade					NS					NS
Poorly differentiated	18	21.2	147	17.1		23	22.3	149	18.1	
Moderately differentiated	49	57.6	512	59.7		59	57.3	509	61.8	
Well differentiated	18	21.2	199	23.2		21	20.4	165	20.0	
MSI					NS					NS
High	6	10.3	76	14.2		5	8.5	79	14.1	
Stable	52	89.7	459	85.8		54	91.5	482	85.9	

Abbreviations: MECC, Molecular Epidemiology of Colorectal Cancer; HRT, hormone replacement therapy; NS, not significant; MSI, microsatellite instability.

(Table 4). Similar results were achieved when calculating the odds ratios from the more detailed data of the pharmacy records of Clalit participants in the study.

Women with a history of HRT use had a somewhat lower proportion of microsatellite instable tumors (10.3% in users according to questionnaire *v* 14.2% in nonusers; 8.5% according to pharmacy records *v* 14.1% in nonusers) but the difference, being based on 82 to 84 instable tumors only, did not reach statistical significance (Table 4).

We evaluated the risk associated with HRT use in a subgroup of carriers of the *APC* premutation I1307K, and did not detect a negative association in this group of 136 carrier women.

Multivariate Analysis

After adjusting for risk factors formerly demonstrated in our study to be associated with the risk of CRC (age, use of aspirin/NSAIDs, use of statins, vegetable consumption, sports activity) the negative association of self-reported HRT use with the occurrence of CRC remained significant (OR, 0.37; 95% CI, 0.22 to 0.62) together with all other variables, excluding vegetables, and including the interactions of HRT with aspirin and sports activity (Table 5).

Table 5. Final Multivariate Analysis Model of the Association of Use of HRT With CRC in Peri/Postmenopausal Female MECC Study Participants

Variable	Peri/Postmenopausal Females (unconditional; n = 1,982)		
	OR	95% CI	*P*
HRT use, ever	0.37*	0.22 to 0.62	
Aspirin use, daily, 3+ years	0.60*	0.45 to 0.79	
Statins use, 5+ years	0.51	0.36 to 0.73	
Family history of CRC, first degree	1.79	1.32 to 2.45	
Sports activity	0.52	0.41 to 0.65	
Vegetables, ≥ 5/d	†		
Age, per year	0.99	0.98 to 0.998	
HRT × aspirin	3.55	1.42 to 8.86	.007
HRT × sports	2.25	1.15 to 4.38	.017

NOTE. Odds ratios shown for variables in final model only.
Abbreviations: MECC, Molecular Epidemiology of Colorectal Cancer; HRT, hormone replacement therapy; CRC, colorectal cancer.
*This model includes an interaction of HRT × aspirin, therefore the aspirin effect is among non-HRT users and the HRT effect is among non-aspirin users.
†Dropped out of final model.

DISCUSSION

Our data indicate that there is a significant inverse association between the risk of CRC and the use of HRT by peri/postmenopausal women. This held true after adjustment for the large variety of risk factors for CRC formerly identified in our study. Our results corroborate the inverse association previously described in case-control and cohort studies as well as randomized controlled studies.[2-11]

We found interesting differences in risk reduction potential by type of HRT preparation. The main effect was found with combined estrogen-progestin oral pills; a nonsignificant risk-reduction was found in estrogen-only pill users, and no effect was found in patch users (mostly estrogen-only patches). Strong negative associations in users of combined preparations were reported from the Women's Health Initiative study[5] and a case-control study.[4] No reduction in risk in estrogen only users was also reported[21,22] although this might have been a function of length of use.[15] Use of transdermal estrogen patch was associated with reduced risk in only one report.[15] While orally administered estrogens are being converted and metabolized in the liver to their conjugated forms that enter the circulation and the bile system, estrogens administered transdermally in the form of a patch are absorbed directly into the systemic circulation and avoid first pass effects. The conjugated metabolites, which are lipid insoluble, are excreted through the biliary system and the conjugates are hydrolyzed in the intestine to active, reabsorbable forms.[23] Several reports have associated gallbladder disease and history of cholecystectomy with the risk of CRC.[24-26] Similarly, gallbladder disease and history of cholecystectomy were also associated with HRT use.[27-31] Transdermal estrogen was shown to have a lesser effect than oral estrogen on the

development of gallbladder disease.[27,31] Other possible explanations for the differential effects of the different types of HRT are that progestins may increase the estrogenic effect of the conjugated estrogen leading to a combination that may be more biologically active in the colon than estrogen alone. Compared with the oral forms of HRT, transdermal estrogen was found to exert only minimal effects on total and free testosterone, thyroxine, and cortisol and their binding proteins.[32]

Of much interest is also the significant interaction between the use of HRT and the use of aspirin observed in our analysis. The strong negative association with CRC risk among aspirin users (mostly of low-dose) was reversed into a positive association when HRT use was also reported. Garcia-Rodriguez et al[33] have recently reported an OR of 0.66 for myocardial infarction in a study of HRT users who did not use NSAIDs that changed into an OR of 1.5 if the HRT users also used NSAIDs or 1.41 if they used 150 mg/d or more of aspirin. While the authors speculated that this cardiac effect could be mediated through cyclooxygenase-2 inhibition, our findings of cancer effects with the use of low-dose aspirin, targeting preferentially cyclooxygenase-1, suggests that the mechanism for interaction of HRT and aspirin/NSAIDs could be different.

The interaction between HRT use and physical activity is hard to explain, as these two behaviors tend to cluster, but has been described by others with regards to other effects of HRT on risk of fractures[34] and on cognition.[35] A recent article[36] suggested that plasma protein carbonyl levels, reflecting oxidative stress levels, were associated with breast cancer risk especially in physically active women and women on HRT, but a strong interaction effect between the latter was noticed.

Our data did not refute formerly published reports suggesting that HRT use did not influence the probability of development of microsatellite instable tumors.[4,37] While one report suggested that the APC D1822V variant was strongly associated with HRT use, no such negative association was found with the *APC* I1307K variant in our study. This particular variant is especially common in the Ashkenazi Jewish population.[38]

A case-control study such as ours could have several limitations. Exposure data were collected retrospectively and are therefore at risk for recall bias. Despite the recent extensive exposure to the issue of risks and benefits of HRT in both the professional and lay literature, the negative association with CRC occurrence was never a major issue in these discussions, thus it is unlikely that participants differentially reported exposures. Our effort to validate the use of HRT through the pharmacy records was only marginally successful, probably because many women in Israel tend to use private gynecologists rather than those provided by the large secondary clinics of the HMO, and buy their HRT products privately. The proportion of validation of HRT use against the pharmacy records was similar in patients and controls (61.6% and 63.8%, respectively). The possibility of selection bias seems unlikely since the rate of HRT use by pharmacy records was similar among the controls who participated and those who declined, all of whom were CHS members. The likelihood that some controls had undiagnosed CRC leading to potential misclassification is small as the study has been active for more than 8 years during which we have encountered only 32 CRC cases among the controls (1.2%). Potential confounders were also of self-report nature; measurement error for these variables could limit our ability to control adequately for confounding.

We found that use of HRT, in the form of oral preparations only, is associated with a 38% relative reduction in the risk of CRC after adjustment for other known risk factors. However, the absence of the risk reduction effect of aspirin in HRT users and the differences in risk reduction with preparation-type call for further study to understand the causes for these phenomena and calls for caution in indicating HRT for CRC prevention.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Gad Rennert, Stephen B. Gruber
Provision of study materials or patients: Gad Rennert, Mila Pinchev
Collection and assembly of data: Gad Rennert, Hedy S. Rennert, Mila Pinchev
Data analysis and interpretation: Gad Rennert, Hedy S. Rennert, Ofer Lavie, Stephen B. Gruber
Manuscript writing: Gad Rennert, Hedy S. Rennert, Ofer Lavie, Stephen B. Gruber
Final approval of manuscript: Gad Rennert, Hedy S. Rennert, Mila Pinchev, Ofer Lavie, Stephen B. Gruber

REFERENCES

1. Jemal A, Siegel R, Ward E, et al: Cancer statistics, 2008. CA Cancer J Clin 58:71-96, 2008

2. Kampman E, Potter JD, Slattery ML, et al: Hormone replacement therapy, reproductive history, and colon cancer: A multicenter, case-control study in the United States. Cancer Causes Control 8:146-158, 1997

3. Nelson HD, Humphrey LL, Nygren P, et al: Postmenopausal hormone replacement therapy: Scientific review. JAMA 288:872-881, 2002

4. Newcomb PA, Zheng Y, Chia VM, et al: Estrogen plus progestin use, microsatellite instability, and the risk of colorectal cancer in women. Cancer Res 67:7534-7539, 2007

5. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al: Women's Health Initiative Investigators: Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med 350:991-1004, 2004

6. Beral V, Banks E, Reeves G: Evidence from andomized trials on the long-term effects of hormone replacement therapy. Lancet 360:942-944, 2002

7. Fernandez E, Gallus S, Bosetti C, et al: Hormone replacement therapy and cancer risk: A systematic analysis from a network of case-control studies. Int J Cancer 105:408-412, 2003

8. Theodoratou E, Campbell H, Tenesa A, et al: Modification of the associations between lifestyle, dietary factors and colorectal cancer risk by APC variants. Carcinogenesis 29:1774-1780, 2008

9. Hoffmeister M, Raum E, Winter J, et al: Hormone replacement therapy, body mass, and the risk of colorectal cancer among postmenopausal women from Germany. Br J Cancer 97:1486-1492, 2007

10. Corrao G, Zambon A, Conti V, et al: Menopause hormone replacement therapy and cancer risk: An Italian record linkage investigation. Ann Oncol 19:150-155, 2008

11. Nanda K, Bastian LA, Hasselblad V, et al: Hormone replacement therapy and the risk of colorectal cancer: A meta-analysis. Obstet Gynecol 93: 880-888, 1999

12. Hannaford P, Elliott A: Use of exogenous hormones by women and colorectal cancer: Evidence from the Royal College of General Practitioners' Oral Contraception Study. Contraception 71: 95-98, 2005

13. Purdue MP, Mink PJ, Hartge P, et al: Hormone replacement therapy, reproductive history, and colorectal adenomas: Data from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (United States). Cancer Causes Control 16:965-973, 2005

14. Gondal G, Grotmol T, Hofstad B, et al: Lifestyle-related risk factors and chemoprevention for colorectal neoplasia: Experience from the

large-scale NORCCAP screening trial. Eur J Cancer Prev 14:373-379, 2005

15. Csizmadi I, Collet JP, Benedetti A, et al: The effects of transdermal and oral oestrogen replacement therapy on colorectal cancer risk in postmenopausal women. Br J Cancer 90:76-81, 2004

16. Mandelson MT, Miglioretti D, Newcomb PA, et al: Hormone replacement therapy in relation to survival in women diagnosed with colon cancer. Cancer Causes Control 14:979-984, 2003

17. Poynter JN, Gruber SB, Higgins PDR, et al: Statins and the risk of colorectal cancer. N Engl J Med 352:2184-2192, 2005

18. Baecke JA, Burema J, Frijters JE: A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr 36:936-942, 1982

19. Yizhaki D, Rennert HS, Rosen G, et al: Validity and reproducibility of a semi-quantitative food frequency questionnaire adapted to an Israeli population. Open Nutr J 2:9-14, 2008

20. Chaiter Y, Rennert G, Fischler R, et al: Dietary intake of carotenoid isomers in Israel. Int J Vitam Nutr Res 77:398-405, 2007

21. Tannen RL, Weiner MG, Xie D, et al: Estrogen affects post-menopausal women differently than estrogen plus progestin replacement therapy. Hum Reprod 22:1769-1777, 2007

22. Anderson GL, Limacher M, Assaf AR, et al: Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. JAMA 291:1701-1712, 2004

23. Medical Pharmacology and Disease-Based Integrated Instruction. http://www.pharmacology2000.com/Gonadal/gonad1.htm

24. Shao T, Yang YX: Cholecystectomy and the risk of colorectal cancer. Am J Gastroenterol 100: 1813-1820, 2005

25. Ekbom A, Yuen J, Adami HO, et al: Cholecystectomy and colorectal cancer. Gastroenterology 105:142-147, 1993

26. Lagergren J, Ye W, Ekbom A: Intestinal cancer after cholecystectomy: Is bile involved in carcinogenesis? Gastroenterology 121:542-547, 2001

27. Cirillo DJ, Wallace RB, Rodabough RJ, et al: Effect of estrogen therapy on gallbladder disease. JAMA 293:330-339, 2005

28. Simon JA, Hunninghake DB, Agarwal SK, et al: Effect of estrogen plus progestin on risk for biliary tract surgery in postmenopausal women with coronary artery disease: The Heart and Estrogen/progestin Replacement Study. Ann Intern Med 135:493-501, 2001

29. Grodstein F, Colditz GA, Stampfer MJ: Postmenopausal hormone use and cholecystectomy in a large prospective study. Obstet Gynecol 83:5-11, 1994

30. Mamdani MM, Tu K, van Walraven C, et al: Postmenopausal estrogen replacement therapy and increased rates of cholecystectomy and appendectomy. CMAJ 162:1421-1424, 2000

31. Liu B, Beral V, Balkwill A, et al: Million Women Study Collaborators: Gallbladder disease and use of transdermal versus oral hormone replacement therapy in postmenopausal women: Prospective cohort study. BMJ 337:a386, 2008

32. Shifren JL, Desindes S, McIlwain M, et al: A randomized, open-label, crossover study comparing the effects of oral versus transdermal estrogen therapy on serum androgens, thyroid hormones, and adrenal hormones in naturally menopausal women. Menopause 14:985-994, 2007

33. García Rodríguez LA, Egan K, FitzGerald GA: Traditional nonsteroidal anti-inflammatory drugs and postmenopausal hormone therapy: A drug-drug interaction? PloS Med 4:e157, 2007

34. Michaëlsson K, Baron JA, Johnell O, et al: Variation in the efficacy of hormone replacement therapy in the prevention of hip fracture. Swedish Hip Fracture Study Group. Osteoporos Int 8:540-546, 1998

35. Etnier JL, Sibley BL: Physical activity and hormone-replacement therapy: Interactive effects on cognition? J Aging Phys Act 12:554-567, 2004

36. Rossner P Jr, Terry MB, Gammon MD, et al: Plasma protein carbonyl levels and breast cancer risk. J Cell Mol Med 11:1138-1148, 2007

37. Slattery ML, Potter JD, Curtin K, et al: Estrogens reduce and withdrawal of estrogens increase risk of microsatellite instability-positive colon cancer. Cancer Res 61:126-130, 2001

38. Rennert G, Almog R, Tomsho LP, et al: Colorectal polyps in carriers of the APC I1307K polymorphism. Dis Colon Rectum 48:2317-2321, 2005

