A Meta-analysis of Hormone Replacement Therapy and Colon Cancer in Women

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Abstract

The influence of endocrine factors on colorectal tumor development remains unclear. We performed a meta-analysis of studies of the association between the use of menopausal hormones and colon cancer in women, published up to December 1996. We derived summary measures of relative risk (RR) by fitting both fixed and random effects models. We also performed analyses by tumor location to the right or left colon, as well as by recency and duration of use. Heterogeneity was assessed according to study design, chronology, or other criteria. Overall, the 20 independent estimates of the association between ever use of menopausal hormones and colon cancer led to a summary RR of 0.85, (0.73, 0.99), using a random effects model. There was substantial heterogeneity among studies. The suggested protective effect of hormones was estimated to be stronger in studies published since 1990 [RR: 0.83, (0.66, 1.04), versus 0.93, (0.78, 1.10), for those published previously]. The estimated RRs were lower among current or recent users [RR: 0.69, (0.52, 0.91)] and among users of more than 5 years [RR: 0.73, (0.53, 1.02)] as compared with short-term users [RR: 0.88, (0.64, 1.21)]. The current state of knowledge suggests a 0–25% risk reduction among ever users of hormone replacement therapy. Inadequate assessment of exposure, poor control of confounding factors, and changing patterns of use over time might have contributed to the slow emergence of this association postulated almost two decades ago. Additional large studies are needed to replicate this finding and explain the exact mechanism of this putative protective effect.

Introduction

The hypothesis of a protective influence of reproductive factors and exogenous hormones on colorectal cancer was first formulated by McMichael and Potter (1). This followed observations of ecological correlation between breast and colon cancer, higher than expected incidence of colorectal (as well as of breast, ovary, and endometrial) tumors among nuns, and descriptive sex- and site-specific data showing a cross-over of colorectal cancer rates around age 50 (2). Women have a similar or higher incidence of colorectal cancer than men before age 50 and a lower incidence thereafter (2). Women also display a higher frequency of right-side tumors than men (2). In addition, although the disease has a sex ratio closer to one than most other cancer sites, women from high-risk areas have recently experienced a sustained decline in mortality, not consistently observed among men (3). In North America, the use of postmenopausal HRT3 peaked in the mid 1970s, after much publicized reports of adverse side effects, including cancer, among long-term users (4, 5). Only recently did it start to rise again (5–7). Epidemiological studies focusing on these products have, therefore, often been impaired by the small available numbers of long-term users.

Studies of the hormonal aspects of colorectal carcinogenesis have attempted to test the original hypothesis that high parity, early first birth, and use of sex hormones were protective against colorectal tumors. In an extensive qualitative review published in 1993, Potter et al. (2) concluded that both parity and age at first pregnancy were likely not associated with risk, whereas the available evidence is suggestive of a risk reduction associated with hormonal replacement. The exact mechanism (direct effect on hormone receptors of the large bowel, modification of bile acids, or other) of this putative protective effect, however, remains unclear (8), as well as the specificity of estrogen and progesterin. Preliminary data suggest that HRT could act quite early in the carcinogenic process, as reflected by its protective association with adenomatous polyps in one recent study (8).

A meta-analysis of all published studies of the association between colorectal tumors and estrogen replacement therapy between 1975 and 1993 (9) led to combined estimates of RRs of 0.91 (0.60, 1.38) in cohort studies and 0.92 (0.71, 1.20) in case-control studies. The possibility of a protective effect, however, has since been reinforced by the publication of a few large additional epidemiological studies, as well as by recent data from the Scandinavian trials suggesting an excess of colorectal cancer [RR: 2.1 (0.8, 5.6) in the Stockholm trial, 1.9 (1.1, 3.3) in all Scandinavian trials combined] among users of adjuvant tamoxifen (10). This finding has not been replicated in other data sets (11). Overall, therefore, the literature on hormones and colorectal cancer is not unanimous.

No adequate randomized controlled trial has thus far been published that would assess this relationship with minimal bias, especially selection bias, although the clinical trial component of the Women’s Health Initiative has the potential for unbiased

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1 Part of this data was presented at the annual meeting of the Society for Epidemiological Research, June 24–26, 1998, Chicago, Illinois.

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3 The abbreviations used are: HRT, hormone replacement therapy; RR, relative risk; OC, oral contraceptives; bmi, body mass index.
assessment of the effects of HRT (12). To update summary estimates of the association between HRT and colon cancer among women, and following the approach suggested by Greenland (13, 14), we have performed a meta-analysis of all studies published on that issue up to December 1996. An important objective of this work was to assess the influence of methodological and design characteristics of published observational studies on summary results and to compare data across categories of users to assess the plausibility of a protective effect.

Materials and Methods

Studies were identified by a computerized search of the Medline and the Cancerlit databases. Key words used in that search included any of the following: colorectal neoplasm or colonic neoplasm or gastrointestinal neoplasm or rectal neoplasm, and estrogen replacement therapy or estrogens or contraceptives, oral. In addition, studies included in the previous meta-analysis from MacLennan et al. (9), and those listed among reference lists from the Internet sites Cancernet and Oncolink or from published studies of the association between HRT and colorectal tumors were included. Only studies published in either French or English up to December 1996 were retained. Unpublished data, including doctoral theses, were excluded. We also excluded three abstracts: the first by Rosenberg et al. (15), because it provided no quantitative measure of effect; the second by Newcomb et al. (16), because it presented interim results of a study (17) subsequently published and included in the analysis; and the third by Grodstein et al. (18), which presented updated results from the Nurses’ Health Study at 12 years of follow-up. Because the previous publication by Chute et al. (19) presented data at 8 years of follow-up for the same cohort but provided more detailed results, only this publication was kept in the analysis. RR estimates for ever use of HRT were, however, very similar in both publications. Two studies (20, 21) based on the same cohort of women from Iowa were published at a 1-year interval. We kept only the most recent one (21). Finally, one study by Wu-Williams et al. (22) included two nonoverlapping study populations recruited in two different geographic areas; both measures of effect were included.

Three aspects of exposure to HRT were assessed: ever versus never use, both jointly and separately for right and left colon; recency of use comparing current and past users; and duration of use contrasting users of more than 5 years with users of shorter duration.

The measure of effect of interest is the RR, approximated by the odds ratio in case-control studies. Summary estimates of RR were first derived using fixed effects models (as described in Refs. 23 and 24). Heterogeneity was assessed using a χ² test for homogeneity with a conservative 10% significance level. Subsequent specific exclusions or subsets of studies were then used to identify significant sources of heterogeneity and to assess methodological or other factors responsible for the differences across studies. Because substantial heterogeneity still remained despite these restrictions, DerSimonian and Laird’s (25) random effects model was fitted to all subsets of studies, and the consistency of the summary estimates of effect under both analytic strategies was evaluated. Random effects models make some provision for both within and across study variability and tend to average the influence of all studies, small and large, on overall summary results. Unless substantial heterogeneity is present, random effects models will provide summary point estimates of effect similar to those of fixed effects models but confidence intervals will be larger (13, 26).

Studies were first grouped according to design. To this end, one small randomized controlled trial (27) was analyzed as a cohort study, and one study (28) whose design seemed unclear was included with the case-control studies. In addition, to assess and minimize the impact of changing patterns of exposure over time, the analysis was restricted to studies published before 1990 (27–35) and subsequently to the most recent ones, published after 1990 (17, 19, 21, 22, 36–41). We did not attempt to assign a quality score to each study. However, the degree of adjustment for confounding was taken into account by performing analyses restricted to those studies that controlled for at least two significant potential confounders, in addition to age (17, 21, 22, 34, 36, 38–41).

This meta-analysis assessed the association between HRT and colon cancer and used data most specific to this relationship. Studies focusing on colorectal tumors as a group were included in this review, but the analysis was also subsequently restricted to those specific to colon cancer. Only one type of exposure by study was assessed, judged to best reflect use of menopausal hormones. However, studies providing only a combined estimate of the effects of different hormonal derivatives (for example, oral contraceptives and HRT, or hormone substitution therapy of any kind) were included in this review. Distinction between contraceptive and noncontraceptive sex hormones has been suggested to be important because both have very different dosages and because they are used by women of different age groups, they could act at different steps of the carcinogenic process (34). Analysis by recency of use compared current or recent use, generally within 1 year, with former use, either at reference date in case-control studies or at baseline in cohort studies. Analysis by duration of use was restricted to those studies that provided data for more and less than 5 years of use. In one study (21), these data were presented only for current users, but still were used in the analysis.

In some studies, stratum-specific adjusted estimates had to be combined. We proceeded as described previously (24, 25) and did not attempt to correct for the dependency of these estimates to a common baseline. We assumed that, as in dose-response analysis, this correction would mostly affect the absolute weighting of a given study and, therefore, the result of the heterogeneity test (42). In all such cases where weights for both crude and adjusted summary RRs were available, they were found to be very similar. In addition, both fixed and random effects models were fitted to all subsets of studies.

Data were analyzed using Microsoft Excel software and other quantitative methods (described in Refs. 23–25, 43, and 44). Except for the assessment of homogeneity, a 5% two-sided significance level was used.

Results

Ever versus Never Use of HRT. Table 1 summarizes the 19 studies, having assessed the relationship between ever use of HRT and colon cancer. These include 8 cohort studies (19, 21, 27, 30, 31, 35–37) with follow-up periods varying between 4 and 14 years and 11 case-control studies (17, 22, 28, 29, 32–34, 38–41). 8 being population-based (17, 22, 29, 32, 33, 38–40) and 3 hospital-based (28, 34, 41). All studies used incident cases, except the one by Calle et al. (36), which focused on fatal cases of colon tumors. One study (29) provided a single estimate of the joint effect of both oral contraceptives and HRT. In addition, three other studies (22, 33, 40) evaluated exposure to non-OC hormones, and it is not clear whether an explicit distinction was made between menopausal hormones and other

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### Table 1  Summary of studies included in the meta-analysis of ever versus never use of HRT and colon cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Location</th>
<th>Study design</th>
<th>Source of subjects</th>
<th>Tumor site</th>
<th>Exposure</th>
<th>Type of hormone</th>
<th>Confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hammond et al.</td>
<td>1979</td>
<td>North Carolina, USA</td>
<td>Case-control</td>
<td>Hospital</td>
<td>Colon and Rectum</td>
<td>Use of ≥ 5 yr</td>
<td>Estrogen replacement therapy</td>
<td>Age, race, yrs of follow-up, history, fat, calcium intake, alcohol, weight 10 yrs ago, activity level, pregnancies, type and age of menopause</td>
</tr>
<tr>
<td>Weiss et al.</td>
<td>1981</td>
<td>Washington St, USA</td>
<td>Case-control</td>
<td>Population</td>
<td>Colon and Rectum</td>
<td>Ever use of ≥ 1 yr</td>
<td>Estrogen replacement therapy</td>
<td>Age</td>
</tr>
<tr>
<td>Potter et al.</td>
<td>1983</td>
<td>Adelaide, Australia</td>
<td>Case-control</td>
<td>Population</td>
<td>Colon</td>
<td>Ever use of any duration</td>
<td>Non-OC hormones</td>
<td>Age</td>
</tr>
<tr>
<td>Davis et al.</td>
<td>1989</td>
<td>Alberta, Canada</td>
<td>Case-control</td>
<td>Population</td>
<td>Colon</td>
<td>Ever use of any duration</td>
<td>OC + HRT</td>
<td>Age, parity, AFLB, hysterectomy, oophorectomy, cholecystectomy, appendectomy</td>
</tr>
<tr>
<td>Furner et al.</td>
<td>1989</td>
<td>Illinois, USA</td>
<td>Case-control</td>
<td>Hospital</td>
<td>Colon and Rectum</td>
<td>Ever use of any duration</td>
<td>Estrogen replacement therapy</td>
<td>Age, parity, AFLB, hysterectomy, oophorectomy, cholecystectomy, appendectomy</td>
</tr>
<tr>
<td>Peters et al.</td>
<td>1990</td>
<td>California, USA</td>
<td>Case-control</td>
<td>Population</td>
<td>Colon</td>
<td>Ever use of any duration</td>
<td>HRT</td>
<td>Age, race, area of residence, history, fat, calcium intake, alcohol, weight 10 yrs ago, activity level, pregnancies, type and age of menopause</td>
</tr>
<tr>
<td>Wu-Williams et al.</td>
<td>1991</td>
<td>Six regions from North America and China</td>
<td>Case-control</td>
<td>Population</td>
<td>Colon</td>
<td>Ever use of any duration</td>
<td>Non-OC hormones</td>
<td>Age, area of residence, % Chinese in area, yrs in NA, saturated fat intake, physical activity</td>
</tr>
<tr>
<td>Gerhardsson de Verdier et al.</td>
<td>1992</td>
<td>Stockholm, Sweden</td>
<td>Case-control</td>
<td>Population</td>
<td>Colon and Rectum</td>
<td>Ever use of any duration</td>
<td>HRT</td>
<td>Age, total energy, fat, protein, fibre intake, bmi, physical activity</td>
</tr>
<tr>
<td>Jacobs et al.</td>
<td>1994</td>
<td>Washington St, USA</td>
<td>Case-control</td>
<td>Population</td>
<td>Colon</td>
<td>Ever use of ≥ 1 yr</td>
<td>Non-OC hormones</td>
<td>Age, education, fibre and calcium intake, alcohol, constipation, bmi, smoking, vitamins, physical activity, intake, physical activity, diet, folate intake</td>
</tr>
<tr>
<td>Newcomb et al.</td>
<td>1995</td>
<td>Wisconsin, USA</td>
<td>Case-control</td>
<td>Population</td>
<td>Colon</td>
<td>Ever use of ≥ 3 mo duration</td>
<td>HRT</td>
<td>Age, sigmoidoscopy, family history, bmi, alcohol, physical activity, diet, folate intake</td>
</tr>
<tr>
<td>Fernandez et al.</td>
<td>1996</td>
<td>Northern Italy</td>
<td>Case-control</td>
<td>Hospital</td>
<td>Colon and Rectum</td>
<td>Ever use of any duration</td>
<td>Estrogen replacement therapy</td>
<td>Age, area of residence, social class, history, age at menarche, parity, total energy intake, consumption of cereals, fruits, vegetables, meat, alcohol, fat, bmi, smoking</td>
</tr>
<tr>
<td>Burch et al.</td>
<td>1979</td>
<td>Tennessee, USA</td>
<td>Cohort</td>
<td>Hospital</td>
<td>Colon</td>
<td>Use of ≥ 5 yr</td>
<td>Estrogen replacement therapy</td>
<td>Age, diagnosis</td>
</tr>
<tr>
<td>Nachtigall et al.</td>
<td>1979</td>
<td>New York City, USA</td>
<td>Randomized clinical trial</td>
<td>Hospital</td>
<td>Colon</td>
<td>Use of 10 yr</td>
<td>Estrogen + progesterone replacement therapy</td>
<td>Age, diagnosis</td>
</tr>
<tr>
<td>Wu et al.</td>
<td>1987</td>
<td>California, USA</td>
<td>Cohort</td>
<td>Population</td>
<td>Colon and Rectum</td>
<td>Ever use of any duration</td>
<td>Estrogens</td>
<td>Age</td>
</tr>
<tr>
<td>Adams et al.</td>
<td>1989</td>
<td>Uppsala, Sweden</td>
<td>Cohort</td>
<td>Population</td>
<td>Colon</td>
<td>Ever use of any duration</td>
<td>Estrogen replacement therapy</td>
<td>Age, bmi</td>
</tr>
<tr>
<td>Chute et al.</td>
<td>1991</td>
<td>USA</td>
<td>Cohort</td>
<td>Population</td>
<td>Colon</td>
<td>Ever use of any duration</td>
<td>Estrogen replacement therapy</td>
<td>Age, race, family history of colon cancer, bmi, consumption of citrus fruits, vegetables, grains, total fat, physical activity, parity, type of menopause, age at menopause, OC, aspirin use, smoking</td>
</tr>
<tr>
<td>Calle et al.</td>
<td>1995</td>
<td>USA</td>
<td>Cohort</td>
<td>Population</td>
<td>Colon</td>
<td>Ever use of any duration</td>
<td>Estrogen replacement therapy</td>
<td>Age, race, family history of colon cancer, bmi, consumption of citrus fruits, vegetables, grains, total fat, physical activity, parity, type of menopause, age at menopause, OC, aspirin use, smoking</td>
</tr>
<tr>
<td>Risch et al.</td>
<td>1995</td>
<td>Saskatchewan, Canada</td>
<td>Cohort</td>
<td>Population</td>
<td>Colon</td>
<td>Ever use of any duration</td>
<td>Estrogen replacement therapy</td>
<td>Age, marital status, physical activity, alcohol use, smoking, bmi, waist/hip ratio, parity</td>
</tr>
<tr>
<td>Folsom et al.</td>
<td>1995</td>
<td>Iowa, USA</td>
<td>Cohort</td>
<td>Population</td>
<td>Colon</td>
<td>Ever use of any duration</td>
<td>HRT</td>
<td>Age, marital status, physical activity, alcohol use, smoking, bmi, waist/hip ratio, parity</td>
</tr>
</tbody>
</table>

*AFLB, age at first live birth; NA, North America.*
types of HRT. Only Newcomb and Storer (17) and Risch and Howe (37) performed detailed analyses by specific sex hormone used. Six studies (28, 30, 32, 34, 39, 41) focused on cancer of the colon and rectum combined, and eight studies (19, 29, 31, 34, 37–40) provided distinct data for the right and left colon. Eleven studies, 5 case-control (28, 29, 32, 33, 38) and 6 cohort (19, 27, 30, 31, 35, 37), found no relationship between use of HRT and colorectal cancer. Among all published studies, only one (22) concluded an increased risk of colon cancer among users of estrogen replacement therapy.

Fig. 1 shows all 20 point estimates of RR, their 95% confidence intervals, as well as the summary estimates obtained with fixed and random effects models. When all studies were combined, the summary RR for ever use of HRT with a fixed effects model was 0.82, (0.76, 0.89). There was, however, substantial heterogeneity across studies. The same was true for most subsets of studies defined by design, chronology, or other criteria (Table 2). Although summary measures of effect varied little in these subanalyses, the lowest estimated RR was observed when the analysis was restricted to the nine studies (17, 21, 22, 34, 36, 38–41) having performed the best adjustment for confounding [random effects model RR: 0.77, (0.60, 0.98)]. The estimated RRs were also smaller in studies (17, 19, 21, 22, 36–41) published after 1990 [random effects model RR: 0.83, (0.66, 1.04)] as compared with before [RR: 0.93, (0.78, 1.10); Refs. 27–35]. Subsequently excluded were the discrepant results of an increased risk associated with exposure in the study by Wu-Williams et al. (22), but it did not completely eliminate the heterogeneity observed across studies. As expected, this led to lower estimates of RR, significant in almost all subgroups (data not shown). With random effects models, these estimated RRs were 0.81, (0.70, 0.93) for all studies combined, 0.69, (0.56, 0.85) for those with better adjustment for confounding, and 0.75, (0.61, 0.92) for the most recent ones published after 1990.

No summary estimate for the association between HRT and colon cancer by tumor location was significantly different from one, for all eight studies having performed analysis by tumor location or for subgroups defined by design or year of publication (data not shown).
**Current versus Past Use of HRT.** Table 3 describes the meta-analysis of the six studies (17, 19, 21, 29, 36, 40) that made a distinction between past and current use of HRT. Both patterns of use were associated with significant reductions in RRs. There was little heterogeneity across studies. The estimated RRs among past users [RR: 0.78, (0.69, 0.88) for all six studies combined, and 0.76, (0.67, 0.87) for those published after 1990] were slightly higher than those for current users which amounted to 0.69, (0.52, 0.88) and 0.76, (0.67, 0.87), respectively.

**Long-versus Short-term Use of HRT.** As illustrated in Table 4, there is a suggestion that the protective effect of menopausal hormones could be more substantial with long-term use than for shorter exposures. There was heterogeneity when all studies having assessed risk by duration of use were grouped, and the RRs with random effects models were estimated at 0.88, (0.64, 1.21) among users of 5 years or less and 0.73, (0.53, 1.02) among users of more than 5 years.

**Discussion**

This meta-analysis of the association between HRT and colon cancer in women suggests a small but still significant protective effect of these products, the estimated summary RR with a random effects model being 0.85, (0.73, 0.99). Although recency confounds duration of use and vice versa, the suggestion of a dose-response gradient in long- as compared with short-term users is compatible with a causal association. Additional studies are needed to estimate summary effects with more precision, to better discriminate between categories of users, and to establish a causal relationship.

There was substantial heterogeneity of effects when studies focusing on ever use were combined using fixed effects models, and although estimates of RR were similar whatever the study design, few groupings of studies were homogeneous enough to allow combination. The same was true when the study of Wu-Williams et al. (22), the only observation of an increased RR among HRT ever users, was excluded. Use of non-OC hormones was reported by 6% and 8% of controls in this study and for 1 year or less by 90% of them. The fact that studies restricted to colon or having performed the best adjustment for confounding still produced heterogeneous results, suggests that some other important conceptual or methodological aspects differ across studies. Assessment of exposure, including the lack of a consistent definition of HRT mostly...
observed in case-control studies, and the quality of information on HRT resulting from faulty recall, as well as differences over time in the patterns of use, especially in the proportion of long-term users, are likely sources of heterogeneity across case-control studies of ever versus never use of menopausal hormones. In fact, all case-control studies have used interview data to define exposure to HRT, whereas two of the cohort studies (31, 37), both of them negative, relied on pharmacy databases. Neither of the two studies, however, was included among studies having performed more extensive adjustment for confounding. The accuracy of questionnaire data on exposure to HRT has been shown to be moderate to good, generally non-differential across categories of subjects and better than recall of exposure to other medications, except oral contraceptives (45–48). Age, interval of the recall period, and duration of use have all been associated with the accuracy of recall (45, 47, 48). Misclassification of exposure could well explain the greater heterogeneity as well as the more conservative RR estimates observed in case-control, as compared with cohort studies. In addition, hormone users are likely to represent a health-oriented group of women and proper adjustment for diet and other aspects of lifestyle, including medical surveillance, is essential to take this healthy user effect into account (6, 7, 49).

This type of selection bias was demonstrated by Sturgeon et al. (50) in an analysis of all-cause and cause-specific mortality associated with menopausal estrogen use among participants in the Breast Cancer Detection Demonstration Project. This study was not included in our review because it had not been identified by our literature search strategy. Its a posteriori inclusion, however, did not substantially modify any summary measure of effect (data not shown).

Our results differ from those of MacLennan et al. (9), who also observed substantial heterogeneity in case-control studies, but a lack of overall association between HRT and colon cancer in a meta-analysis of studies published up to 1993. Their work included only five studies published after 1990 and, more specifically, none of the five recent ones (17, 21, 36, 40, 41) with large numbers of subjects and a more comprehensive adjustment for confounding factors. We did not attempt to include unpublished data in this review because we believe that the time and work required to do so would be substantial, while the assurance that all material had been gathered could not be met. In addition, unpublished studies may be more likely to be methodologically weaker, although surveys on this issue do not consistently suggest so (51). Quality, sample size, and source of funding have been reported to be important predictors of publication for clinical trials (51). Because the best designed and larger studies in this meta-analysis jointly produced the smallest summary estimates of effect, inclusion of unpublished material would likely influence our results toward the null. Although publication bias remains a possibility, and might be responsible for the trend toward stronger effects observed in subgroup analyses by recency or duration of use, the consistency of the evidence, especially the direction of observed associations across studies and overall, should be seen as an indication of the validity of our results (52).

The meta-analysis of observational studies has been the object of an intense debate (53, 54). Although the technique is specifically conceived and used to detect small effects, heterogeneity is a central threat to its validity and several methods have been proposed to deal with it appropriately (55). Few subsets of publications were homogeneous enough to allow use of fixed effects models in the analysis of ever use of HRT. That is why we used and compared both fixed and random effects models, which we feel is a more adequate solution for dealing with heterogeneous material than excluding specific studies when there is no strong methodological argument to do so (55).

Overall, our analysis suggests a 0–25% risk reduction associated with ever use of HRT. In recent years, a considerable shift of attitudes toward HRT at menopause has taken place. In 1992, 29% of female respondents ages 45–64 years to the Quebec Health Survey (56) were using hormonal preparations to control menopausal symptoms or for other reasons, a 7% increase as compared with the 1987 survey (57). For women over 65-years-old, these proportions were 10% and 7%, respectively. Although women are not likely to start using HRT to reduce their risk of colon cancer, establishing this chemopreventive property of menopausal hormones could help put into perspective the small increase in breast cancer risk reported in many studies (58, 59) as well as other important health outcomes, such as cardiovascular disease, osteoporosis, and quality of life, in the decision to use or not use these products.

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