Hormone Replacement Therapy and Adenoma Recurrence: Implications for Its Role in Colorectal Cancer Risk

María Elena Martínez

In this issue of the Journal, Woodson et al. (1) present findings on the role of hormone replacement therapy (HRT) and the risk of adenoma recurrence from a prospective study nested in the Polyp Prevention Trial (PPT). Their results show that current HRT use is not associated with recurrence of adenomatous polyps. However, the investigators did observe a statistically significant interaction by age. Among women aged 62 years and older, an inverse association between HRT use and the risk of adenoma recurrence was shown (odds ratio [OR] = 0.58; 95% confidence interval [CI] = 0.35 to 0.97), whereas among women aged less than 62 years, an increased risk was observed (OR = 1.99; 95% CI = 1.11 to 3.55). There was also a suggestion of a negative association between HRT use and the risk of distal adenomas and a positive association between HRT use and the risk of proximal adenomas.

The results of the study by Woodson et al. (1) do not support the majority of the published literature regarding HRT use and colorectal cancer. For example, when compared with never use, ever use of HRT is associated with a 20% reduction in the risk of colon cancer, and current use is associated with a 30% reduction in risk (2). The few existing case–control studies (3–5) regarding adenoma prevalence also support an inverse association between HRT use and the risk of colorectal adenoma. The results of the study by Woodson et al. (1) are, however, supported by those of the Nurses’ Health Study (6), a prospective study of 21,153 women who underwent a colonoscopy or sigmoidoscopy for screening purposes and in whom 838 women had distal adenomatous polyps during 14 years of follow-up. In the Nurses’ Health Study (6), no association was observed between current HRT use and the relative risk (RR) of adenomas (RR = 0.91; 95% CI = 0.77 to 1.08). However, there was a statistically significant inverse association between HRT use and the risk of adenomas 1 cm or larger in size (RR = 0.74; 95% CI = 0.55 to 0.99). It was not possible to test the same hypothesis in the PPT (1) because of the small number of large recurrent adenomas.

Because the study by Woodson et al. (1) was nested within a trial of adenoma recurrence, a common study design for colorectal cancer chemoprevention, the study population comprises individuals with a history of adenomatous polyps. After a cleanout colonoscopy for the removal of potentially missed polyps, participants were followed for 3 years, at which time they underwent an end-point colonoscopy for the detection of additional adenomas. In the present study, enrollment was restricted to women in whom an adenomatous polyp had already formed. However, at baseline or enrollment, approximately 40% of the women had developed an adenoma while receiving HRT. Thus, an argument can be made that these are women who had already undergone the initiation-phase of carcinogenesis and, furthermore, that HRT was not highly protective against the formation of a baseline adenoma.

Although studies of adenoma recurrence, such as the PPT, have their limitations, they also have their strengths (Table 1). Because adenomas are frequently asymptomatic, etiologic studies mostly deal with prevalent lesions that were probably formed years to decades before their diagnosis. Consequently, epidemiologic studies, even prospective studies of newly diagnosed adenomas, cannot ascertain whether the exposure factor preceded the onset of adenoma formation. Therefore, in the setting of chemoprevention trials, such as the PPT, where all of the detected adenomas are resected at baseline, it is possible to prospectively assess the roles of risk factors in the etiology of adenoma formation. Another major strength is the completeness in follow-up, with a high rate of participants undergoing follow-up colonoscopy and, thus, minimizing detection bias. Although the adenoma recurrence trial design provides a convenient model in which to test various interventions, a major limitation is the inability to assess the role of risk factors at earlier or later stages in the pathway of colorectal carcinogenesis. Specifically, the results of these trials do not provide evidence for the role of agents in the occurrence of new or initial adenomas. Perhaps more important, adenoma recurrence studies usually do not have the necessary statistical power to assess whether a factor is related to the development of large or dysplastic lesions, a limitation identified by Woodson et al. (1). In addition, because participants are followed for a short period of time from exposure to ascertainment of recurrence (approximately 3 years), it is unclear whether this period of time is sufficient or biologically important for studies of risk factors, such as HRT use. It is entirely possible that null findings are the result of an inadequate length of follow-up period and, therefore, do not exclude the role of HRT use in offering protection against the risk of colorectal neoplasia.

The results of the study by Woodson et al. (1) do not provide supportive evidence for a protective role of HRT use and adenoma recurrence. However, these data should be put in perspective relative to those of published results (2) for colorectal cancer. Commonly used agents, such as aspirin and postmenopausal estrogens, have potential adverse effects and benefits beyond prevention of colorectal neoplasia, including an increased risk of breast cancer and a decreased risk of coronary heart disease. Therefore, the results of the study by Woodson et al. (1) should also be considered in light of the overall risks and benefits associated with HRT.

Because no single study or study setting can provide conclusive evidence regarding the etiology of colorectal cancer, it is important to test new and existing hypotheses in different study...
settings. Conducting studies of adenoma recurrence can, therefore, make important contributions. There is no doubt that numerous analyses pertaining to the observational component of completed adenoma recurrence trials are forthcoming. Results of these valuable data must be interpreted in light of their strengths and limitations and in accordance with existing data from studies of colorectal cancer end points.

**REFERENCES**


<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective nature of data</td>
<td>Selectivity of population and limited generalizability</td>
</tr>
<tr>
<td>Investigation of etiology of adenoma formation</td>
<td>Assessment of premalignant lesion rather than invasive cancer</td>
</tr>
<tr>
<td>Detection bias minimized</td>
<td>Investigating risk factors related to early events in carcinogenesis sequence</td>
</tr>
<tr>
<td>Relatively short follow-up period needed for end point analyses</td>
<td>Short duration in follow-up from exposure to end point</td>
</tr>
</tbody>
</table>