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Differences in Colon Adenomas and Carcinomas Among Women and Men Potential Clinical Implications

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Colorectal cancer remains the third leading cause of cancer deaths among women and men in the United States, underscoring the need for more effective preventive strategies for both sexes. Many promising approaches are based on the adenoma-carcinoma paradigm of colon carcinogenesis. The clinical corollary to this model is that the presence of adenomas represents a robust marker of colon carcino-genesis. This leads to 2 distinct applications for colorectal cancer prevention: target for intervention and risk marker. Indeed, removing adenomas through colonos-copy has been shown to decrease future colorectal cancer occurrence by 75% to 90%. From a screening perspective, the colonoscopic adenoma identification is used clinically to gauge long-term risk and dictate the frequency of future colorectal cancer screening.

Most data suggest that the effect of colorectal cancer is approximately equivalent in both sexes. In 2009, an estimated 71 380 women and 75 590 men will develop colorectal cancer.[1] This is consistent with data from 1993-2003 in which women composed 50% of patients in an unselected cohort of 161 172 patients with colorectal cancer from US community cancer centers.[2] Moreover, while estimates of incidence of colorectal cancer has suggested up to a 2-fold male predominance,[3] the more robust lifetime risk estimates for US women and men are comparable (5.1% vs 5.5%, respectively).[1] Taken together, this and other evidence would suggest that colorectal cancer is, by and large, a sex-neutral malignancy. Therefore, it would logically follow that colonic adenomas should also be equivalent in women and men.

However, several large-scale studies have indicated that women have a substantially lower adenoma detection rate than men. For instance, in a cross-sectional analysis of 50 148 patients undergoing colonoscopy-based screening program, Regula et al[4] demonstrated that, compared with women, men had an adjusted odds ratio for advanced adenomas of 1.73 (95% confidence interval [CI], 1.52-1.98). Additionally, Schoenfeld et al[5] noted that the relative risk (RR) of clinically significant neoplasia (advanced adenomas) in men was 1.91 (95% CI, 1.42-2.56) compared with women. In a recent meta-analysis including 924 932 adults, Nguyen et al[3] reported that the RR of advanced neoplasia in men vs women was 1.83 (95% CI, 1.69-1.97).

These findings would imply that adenomas (even those designated as advanced, ie, size ≥1 cm or high-grade dysplasia or ≥25% villous features) represent a less reliable marker of colorectal cancer risk in women than in men, and would lead to speculation that

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colonoscopic identification of adenomas may be less protective of colorectal cancer in women than in men. Although rigorous evidence for this hypothesis is lacking, an administrative database review by Bressler et al[6] noted that women were 41% more likely than men to develop colorectal cancer despite undergoing colonoscopy (4.1% vs 2.9%, *P*<.001). Other supportive evidence centers on the predilection for proximal lesions among women.[5] Baxter et al[7] demonstrated that even though having a colonoscopy was associated with decreased risk of subsequent colorectal cancer by two-thirds in the distal colon, no protective effect was found for lesions in the proximal colon. These studies suggest that the lower prevalence of adenomas in women may translate into possibly less efficacy of colonoscopy.

There is biological precedence for the sex-related differential clinical behavior of colonic neoplasia. Randomized controlled studies have demonstrated the chemopreventive abilities of estrogens/progesterones, potentially mediated by the tumor suppressor role of estrogen receptor β.[8] Moreover, numerous studies have documented the higher proportion of microsatellite-unstable (MSI-high) lesion in women consonant with their slightly better prognosis.[9] From a risk factor perspective, women appear to have differential sensitivity to the carcinogenic effect of cigarette smoking.[2] From an epidemiological perspective, women develop more proximal colorectal cancer, but lesions generally occur somewhat later in life compared with men (1.9-3.4 years).[2] In this regard, the population-based cancer registry review by Brenner et al[10] indicated that the age of onset differential between the sexes was even greater (4-8 years), suggesting the potential ramifications for age of screening initiation. Thus, credible biological underpinnings exist for a sex-related difference in colon carcinogenesis.

There are several potential explanations for the observation that women have fewer adenomas but a roughly equivalent number of colorectal cancers as men. One possibility is that women have relatively less tumor initiation but a greater proportion of lesions that undergo progression. Using data from the Women's Health Initiative, Chlebowski et al[8] reported that women randomized to receive estrogen/progesterone had a lower rate of colorectal cancer (hazard ratio, 0.56; *P*=.003) but a greater number of positive lymph nodes than women in the placebo group (mean [SD], 3.2[4.1] vs 0.8 [1.7], respectively; *P*=.002), and generally had more advanced lesions (regional or metastatic involvement, 76.2% vs 48.5%; *P*=.004). Another possibility is that women are more likely to develop colorectal cancer through nonpolypoid mechanisms. Although these “flat and depressed lesions” have increasingly been recognized, there is no compelling data to date to suggest a sex predilection.

Moreover, risk factors such as diet or tobacco use may be quite distinct between men and women leading to differential manifestations on colon carcinogenesis. In addition, it is possible that because women tend to live longer than men, women may have a lower polyp incidence (point of time measurement) but equivalent lifetime prevalence. However, the effect size (5% increased lifespan) seems unlikely to explain the approximately 80% difference in adenoma detection rates.[3] Furthermore, when the data are assessed in toto, the RR of advanced adenomas in men vs women appeared comparable over a wide range of ages and was comparable for those aged 40 to 49 years (RR, 1.53; 95% CI, 1.23-1.91) and for those older than 70 years (RR, 1.53; 95% CI, 1.26-1.86).[3]

Regardless of etiology, there are 2 major potential clinical implications for the adenoma-carcinoma rate discordance among women. Given the lower adenoma incidence, some argue for less intensive screening of women.[3,4] However, this approach ignores the roughly equivalent colorectal cancer risk. It would be more prudent to consider viewing sex through the prism of risk stratification, focusing on the most clinically meaningful end point,

colorectal cancer. This would have implications in several facets of colorectal cancer prevention efforts in women. First, colonoscopy (either negative or with polypectomy) may not portend the same long-term risk reduction for women as for men. Second, adenomas are frequently used as biomarkers for colon carcinogenesis for various interventions (eg, chemoprevention trials) and for risk factor analysis (eg, diet, smoking). Therefore, these studies may need to be separately analyzed and validated in women.

In conclusion, available data suggest a significant discordance between lifetime prevalance of colorectal cancer and incidence of adenomas between men and women. The inescapable but unconventional conclusion is that adenomas are a less robust marker of colorectal cancer risk in women than in men. From a clinical perspective, the implication is that lower prevalence of adenoma may not portend the same long-term risk reduction in women as in men. This factor may be a plausible reason to explain recent reports regarding the suboptimal ability of colonoscopy to protect against proximal colorectal cancer. This concept needs to be confirmed before recommending any change in current screening guidelines such as potentially initiating screening later in women (given later age of cancer) but more frequent testing given the inferior negative predictive value for women who are adenoma-free.

In the interim, the adenoma-carcinoma paradox needs to be factored into design and interpretation of risk factor and chemoprevention studies. Furthermore, although still preliminary, it may be reasonable to consider the discordance in the adenoma-carcinoma prevalence as one factor in the comprehensive risk determination for colon carcinogen-esis and the individualization of colorectal cancer prevention strategies.

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REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA Cancer J Clin 2009;59(4):225–249. [PubMed: 19474385]
2. Zisman AL, Nickolov A, Brand RE, Gorchow A, Roy HK. Associations between the age at diagnosis and location of colorectal cancer and the use of alcohol and tobacco: implications for screening. Arch Intern Med 2006;166(6):629–634. [PubMed: 16567601]
3. Nguyen SP, Bent S, Chen YH, Terdiman JP. Gender as a risk factor for advanced neoplasia and colorectal cancer: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2009;7(6): 676–681. [PubMed: 19514116]
4. Regula J, Rupinski M, Kraszewska E, et al. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. N Engl J Med 2006;355(18):1863–1872. [PubMed: 17079760]
5. Schoenfeld P, Cash B, Flood A, et al. Colonoscopic screening of average-risk women for colorectal neoplasia. N Engl J Med 2005;352(20):2061–2068. [PubMed: 15901859]
6. Bressler B, Paszat LF, Chen Z, et al. Rates of new or missed colorectal cancers after colonoscopy and their risk factors: a population-based analysis. Gastroenterology 2007;132(1):96–102. [PubMed: 17241863]
7. Baxter NN, Goldwasser MA, Paszat LF, et al. Association of colonoscopy and death from colorectal cancer. Ann Intern Med 2009;150(1):1–8. [PubMed: 19075198]
8. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med 2004;350(10):991–1004. [PubMed: 14999111]

9. Kennelly R, Kavanagh DO, Hogan AM, Winter DC. Oestrogen and the colon: potential mechanisms for cancer prevention. Lancet Oncol 2008;9(4):385–391. [PubMed: 18374292]

10. Brenner H, Hoffmeister M, Arndt V, Haug U. Gender differences in colorectal cancer: implications for age at initiation of screening. Br J Cancer 2007;96(5):828–831. [PubMed: 17311019]