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Endometrial Cancer Chemoprevention: Implications of Diverse Pathways of Carcinogenesis

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Abstract Endometrial cancers may be divided into two groups, reflecting differences in clinical behavior and pathogenesis. Endometrioid adenocarcinoma, which accounts for the majority of endometrial cancers, typifies the group of endometrial carcinomas that develop from atypical endometrial hyperplasia in the setting of excess estrogenic stimulation. In contrast, serous carcinomas are representative of endometrial tumors that occur in older women who have endometrial atrophy and lack the typical endometrial cancer risk factors reflecting unopposed estrogen exposure. Serous carcinomas are frequently associated with p53 abnormalities and appear to develop from a surface lesion termed endometrial intraepithelial carcinoma. Although serous carcinomas are rare, these highly aggressive tumors account for a disproportionate number of endometrial cancer deaths. Further delineation of the estrogen-dependent and estrogen-independent pathways of endometrial carcinogenesis may be useful in developing comprehensive chemopreventive approaches for endometrial cancer.

Key words: Carcinogenesis, carcinoma, endometrioid, hyperplasia, intraepithelial, p53, serous

The development of effective chemoprevention for endometrial cancer requires a comprehensive understanding of endometrial carcinogenesis. Proposed chemoprevention strategies have been based on the observation that exposure to estrogen, with insufficient progestational stimulation, predisposes women to develop atypical endometrial hyperplasia and carcinoma. Although estrogen exposure is clearly linked to endometrial cancer, recent studies suggest that endometrial cancers are heterogeneous with respect to clinical behavior and pathogenesis [1,2]. Endometrioid carcinomas, which account for about 80% of endometrial cancers, are indolent neoplasms that often develop from atypical endometrial hyperplasia in the setting of unopposed estrogen exposure. However, serous carcinoma, and possibly other aggressive tumor types, appear to develop in an estrogen-independent manner. Although these tumors comprise a minority of endometrial cancers, they account for a disproportionate number of endometrial cancer deaths.

In this review, the distinguishing features of estrogen-related and -unrelated neoplasms will be presented using endometrioid and serous carcinomas, respectively, as typical examples of these two groups. A dualistic model of endometrial carcinogenesis is proposed and the implications of this model for cancer chemoprevention are presented [3].

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EPIDEMIOLOGY

In a recently performed case-control study of nearly 400 tumors, marked obesity, use of exogenous estrogen, early menarche, and diabetes were identified as risk factors for the development of endometrioid carcinoma [4]. Apart from early menarche, none of these factors were associated with serous carcinoma. Oral contraceptive use, multiparity, and current smoking were associated with a decreased risk of developing endometrioid carcinoma. Oral contraceptives and current smoking were also associated with a reduced risk for developing serous carcinoma, but the protective effect for contraceptives appeared weaker. In light of the small number of serous carcinomas studied, this effect will have to be confirmed by larger studies. In summary, exogenous hormone use and conditions reflecting hyperestrogenism, such as obesity, were risk factors for the development of endometrioid carcinoma, but were unrelated to serous carcinoma.

CLINICAL FEATURES

The median age for women with serous carcinomas is five to ten years later than that for endometrioid carcinomas. In a recent clinicopathologic study, 85% of endometrioid carcinomas presented with Stage I disease compared to 13% of serous carcinomas. Tumor-related deaths occurred in 25% of endometrioid cancer patients compared to 64% of women with serous carcinomas [5]. In this study, cases of atypical hyperplasia were excluded by pathology review. Given the frequency with which atypical hyperplasia is misinterpreted as carcinoma, it is likely that the overall difference in mortality related to endometrioid and serous carcinomas would be even greater in community practice. In addition to differences in survival, the pattern of spread in endometrioid and serous carcinomas is also different. Metastatic endometrioid carcinoma usually appears as discrete, solid nodules, whereas serous carcinoma often produces peritoneal studding with encasement of organs resembling ovarian carcinoma. Finally, serous carcinomas with little or no myometrial invasion may present with disseminated disease, whereas depth of myometrial invasion is one of the most important prognostic factors in endometrial carcinomas [6–8].

HISTOPATHOLOGY

Although both endometrioid and serous carcinomas may be composed of glands and papillary structures, the appearance of these tumors is quite distinctive. The cardinal feature distinguishing these neoplasms is that in endometrioid carcinomas, the architectural and nuclear grade usually correspond, whereas in serous carcinomas, areas composed of well-formed glands and papillae (grade 1 architecture) are associated with grade 3 nuclear atypia [7,9]. Since serous carcinomas by definition display high-grade nuclear atypia and have a poor prognosis, grading has little prognostic value. In contrast, grading has significant predictive value in endometrioid carcinomas. Grade 3 endometrioid carcinomas are generally larger than grade 1 tumors, suggesting that poorly differentiated endometrioid carcinomas arise from smaller, well-differentiated tumors.

POTENTIAL PRECURSORS

Endometrial Hyperplasia

Evidence establishing atypical endometrial hyperplasia as an immediate cancer precursor includes its frequent coexistence with endometrioid carcinoma and the morphologic similarity and topographic proximity of hyperplasia and endometrioid carcinoma when present concurrently [10–16]. In addition, both lesions appear to be related to unopposed estrogen stimulation and may be inhibited with progestational agents [17]. Finally, progression to carcinoma is identified in 25% of untreated atypical hyperplasias. Because estrogen is a potential promoter of endometrial carcinogenesis but probably not a carcinogen, it is not surprising that progestational agents inhibit the growth of atypical endometrial hyperplasia and carcinoma, but do not completely reverse many of these lesions [19].

Endometrial Intraepithelial Carcinoma

Endometrial intraepithelial carcinoma (EIC) is a recently described lesion defined as replacement of benign endometrial surface epithelium and glands by malignant cells resembling high-grade carcinoma. In a recent study, EIC was found in 89% of serous carcinomas compared to

6% of endometrioid carcinomas. In approximately half of the serous carcinomas, EIC was extensive and multifocal, whereas in endometrioid carcinomas, EIC was always limited in extent and immediately adjacent to the invasive neoplasm [5].

The appearance and frequent identification of EIC adjacent to invasive carcinoma is consistent with the concept that EIC represents a pattern of intramucosal tumor spread. Substantial evidence supports the view that EIC is a precursor of invasive serous carcinoma [5,7]. First, EIC is strongly and specifically associated with serous carcinoma. Second, the abrupt transition between EIC and benign-appearing mucosa resembles *in situ* carcinoma of the endocervix, fallopian tube, and other sites. Third, EIC is often multifocal and non-contiguous with invasive carcinoma; similar *in situ* lesions can be identified in the endocervix, fallopian tube, and surface epithelium of the ovary. Fourth, EIC and serous carcinoma have similar patterns of p53 expression. Finally, and most important, EIC has been found in patients with microscopic, minimally invasive tumors and in women without invasive carcinomas. The presence of lesions resembling EIC in extrauterine sites may account for the high rate of recurrence in patients presenting with clinical Stage I disease.

In summary, EIC is a distinctive morphologic lesion strongly and specifically associated with serous carcinoma. Our observations suggest that EIC represents a distinctive pattern of intramucosal spread and very likely represents the precursor of serous carcinoma.

p53 ABNORMALITIES

Immunohistochemical studies have demonstrated that p53 abnormalities occur in 86% of serous carcinomas compared to 20% of endometrioid carcinomas. Most endometrioid carcinomas that demonstrate p53 abnormalities are high grade [3]. Normal endometrium and endometrial hyperplasia are not immunoreactive for p53 protein; p53 mutations have not been found in endometrial hyperplasia using a polymerase chain reaction-based technique [21]. In contrast, every example of EIC associated with a p53 immunoreactive invasive carcinoma was also immunoreactive in one study [3]. Abnormal expression of p53 protein has also been demonstrated in two of three lesions identified in patients without invasive carcinoma [unpublished observation]. These findings suggest that p53 mutation is unrelated to the development of endometrioid carcinoma from endometrial hyperplasia. In contrast, the consistent demonstration of p53 abnormalities in EIC, including lesions with minimal or no myometrial invasion, suggests that p53 abnormalities occur early in the development of serous carcinoma.

A DUALISTIC MODEL OF ENDOMETRIAL CARCINOGENESIS

Endometrial cancers appear to develop via two different pathways [3].

Estrogen-Dependent Pathway

The development of endometrioid carcinoma is related to prolonged stimulation by unopposed estrogen. In this pathway, cancers develop from endometrial hyperplasia that has slowly developed increasing degrees of architectural and cytologic atypia over time. This multistep pathway appears analogous to the development of adenocarcinoma from colonic polyps. Point mutations in the *ras* gene have been identified in a minority of endometrial hyperplasias and endometrioid carcinomas, suggesting a role for this genetic abnormality in malignant transformation [21–24]. However, the events that lead to morphologically recognizable carcinoma are unknown. Although estrogen is strongly implicated as a promoter in the development of endometrioid carcinoma, the initiators of carcinogenesis in this pathway have not been identified. Since p53 mutations are rare in grade 1 endometrioid carcinomas and not described in hyperplasia, p53 mutation appears unrelated to the early development of endometrioid carcinoma. Maintenance in p53 function in endometrial hyperplasia may explain why endometrioid carcinomas develop slowly. The identification of p53 abnormalities in grade 3 endometrioid carcinomas suggests a role for p53 mutation in dedifferentiation in a minority of these tumors.

Estrogen-Independent Pathway Associated With p53 Mutation

Serous carcinomas generally arise from atrophic endometrium and are almost never associ-

ated with endometrial hyperplasia. Assuming that all invasive carcinomas arise from an *in situ* lesion, it is plausible that in the estrogen-independent pathway, malignant transformation occurs in a cell or cells contained within benign atrophic or inactive endometrium. Abnormal p53 expression appears to represent an early event that occurs in conjunction with the development of EIC. Although serous carcinomas may contain estrogen receptors, these tumors are not associated with unopposed estrogen exposure or endometrial hyperplasia and do not respond to progestational agents [25,26]. Endometrial intraepithelial carcinoma and p53 abnormalities have been found in serous carcinoma as well as other aggressive endometrial neoplasms, suggesting an important role for EIC and p53 in a subset of endometrial cancers.

CHEMOPREVENTION OF ENDOMETRIAL CANCER

A significant proportion of endometrioid carcinomas appear to develop from estrogen-induced, atypical endometrial hyperplasia. Epidemiologic studies demonstrate that women using oral contraceptives containing progestins have a reduced risk of developing these tumors. Therefore, administration of progestins could potentially reduce the incidence of atypical endometrial hyperplasia and, consequently, endometrioid carcinoma. However, it is noteworthy that the majority of endometrioid cancers present as curable Stage I neoplasms. Thus, the benefit achievable through implementation of such a chemopreventive approach must be weighed against the potential morbidity associated with hormonal therapy, including growth-promoting effects on breast cancer, especially in young women, and thrombotic cardiovascular complications in smokers over the age of 35.

In 50% of women with endometrioid carcinoma, endometrial hyperplasia is not identified [5]. Although risk factors for endometrioid carcinomas associated with hyperplasia appear similar to those which are not associated with hyperplasia, it remains possible that some endometrioid carcinomas develop in an estrogen-independent manner and would not be prevented with oral contraceptive use [4]. In addition, the development of serous carcinoma appears to be unrelated to estrogen. Our data suggest that oral contraceptive use may be protective for serous carcinoma, but the effect is weak and should be confirmed in larger series. Serous carcinomas and other aggressive variants of endometrial cancer are comparatively rare, but since these neoplasms produce a disproportionate number of endometrial cancer deaths, they are nonetheless quite important. In fact, the original description of serous carcinoma by Hendrickson *et al.* [9] was prompted by a retrospective study revealing that serous carcinomas comprised only 10% of clinical Stage I endometrial carcinomas, but accounted for 50% of relapses in these patients. These findings have been confirmed subsequently by numerous other investigations [6–8]. Thus, chemoprevention using hormonal agents is likely to reduce incidence rates of endometrial cancer without making a significant impact on mortality rates.

Several measures to reduce endometrial cancer rates are already available without administration of drugs, namely weight control and exercise [27]. Furthermore, development of improved methods for administering post menopausal hormones and for monitoring patients receiving these agents may also reduce rates of adenocarcinoma in these women. Finally, educating pathologists concerning the need to employ stringent criteria for diagnosing endometrial carcinoma in curettage and biopsy specimens would prevent overdiagnosis, and consequently, overtreatment of hyperplastic lesions.

The development of chemoprevention strategies for endometrial cancer would be advanced by research elucidating mechanisms of endometrial carcinogenesis. Future studies correlating histopathology and molecular biology may enhance our understanding of endometrial carcinogenesis and permit a rational approach to effective chemoprevention.

REFERENCES

1. Bohkman JV: Two pathogenetic types of endometrial carcinoma. Gynecol Oncol 15:10–17,1983.
2. Deligdisch L, Cohen CJ: Histologic correlates and virulence implications of endometrial carcinoma associated with adenomatous hyperplasia. Cancer 56:1452–1455, 1985.
3. Sherman ME, Bur ME, Kurman RJ: p53 protein expression in endometrial tumors and their putative precursors. Mod Pathol 8:97A, 1995.
4. Sherman M, Sturgeon S, Brinton L, Berman M,

Mortel R, Twiggs L, Barrett R, Wilbanks G: Endometrial cancer risk factors differ by histopathologic type. Mod Pathol 8:97A, 1995.
5. Ambros RA, Sherman ME, Zahn CM, Bitterman P, Kurman RJ: Endometrial intraepithelial carcinoma: A distinctive lesion specifically associated with tumors displaying serous differentiation. Hum Pathol, 1995 (in press).
6. Lee KR, Belinson JL: Recurrence in non-invasive endometrial carcinoma. Relationship to uterine papillary *serous* carcinoma. Am J Surg Pathol 15:965–973, 1991.
7. Sherman ME, Bitterman P, Rosenshein NB, Delgado G, Kurman RJ: Uterine serous carcinoma: A morphologically diverse neoplasm with unifying clinicopathologic features. Am J Surg Pathol 16:600–610, 1992.
8. Silva EG, Jenkins R: Serous carcinoma in endometrial polyps. Mod Pathol 3:120–128, 1990.
9. Hendrickson M, Ross J, Eifel P, Martinez A, Kempson R: Uterine papillary serous carcinoma: A highly malignant form of endometrial adenocarcinoma. Am J Surg Pathol 6:93–108, 1982.
10. Taylor H: Endometrial hyperplasia and carcinoma of the body of the uterus. Am J Obstet Gynecol 23:309–322, 1932.
11. Gusberg SB, Moore DB, Martin F: Precursors of corpus cancer. II. A clinical and pathologic study of adenomatous hyperplasia. Am J Obstet Gynecol 68:1472–1488, 1954.
12. Cullen TS: Cancer of the uterus. Its pathology, symptomatology, diagnosis and treatment; also the pathology of diseases of the endometrium. 1st ed. Philadelphia: W.B. Saunders, Co., 1900.
13. Novak E, Yui E: Relation of endometrial hyperplasia to adenocarcinoma of the uterus. Am J Obstet Gynecol 32:674–698, 1936.
14. Novak E, Rutledge F: Atypical endometrial hyperplasia simulating adenocarcinoma. Am J Obstet Gynecol 55:46–63, 1948.
15. Hertig AT, Sommers SC: Genesis of endometrial carcinoma. I. Study of prior biopsies. Cancer 2:946–956, 1949.
16. Welch WR, Scully RE: Precancerous lesions of the endometrium. Hum Pathol 9:503–512, 1977.
17. Deligdisch L: Morphologic correlates of host response in endometrial carcinoma. Am J Reprod Immunol 2:54–57, 1982.
18. Kurman RJ, Kaminski PF, Norris HJ: The behavior of "untreated" hyperplasia in 170 patients. Cancer 56:403–412, 1985.
19. Ferenczy A, Gelfand M: The biologic significance of cytologic atypia in progesterone-treated endometrial hyperplasia. Am J Obstet Gynecol 160:126–131, 1989.
20. Kohler MF, Nishii H, Humphrey PA, Saski H, Marks J, Bast RC, Clarke-Pearson DL, Boyd J, Berchuk A: Mutation of the p53 tumor-suppressor gene is not a feature of endometrial hyperplasia. Am J Obstet Gynecol 169:690–694, 1993.
21. Boyd J, Risinger JI: Analysis of oncogene alterations in human endometrial carcinoma: Prevalence of *ras* mutations. Mol Carcinog 4:189–195, 1991.
22. Enomoto T, Inoue M, Perantoni AO, Buzard GS, Miki H, Tanizawa O, Rice JM: K-*ras* activation in premalignant and malignant epithelial lesions of the human uterus. Cancer Res 51:5308–5314, 1991.
23. Sasaki H, Nishii H, Takahashi H, Tada A, Furusato M, Terashima Y, Siegal GP, Parker SL, Kohler MF, Berchuk A, Boyd J: Mutation of the Ki-*ras* protooncogene in human endometrial hyperplasia and carcinoma. Cancer Res 53:1906–1910, 1993.
24. Ignar-Trowbridge P, Risinger JI, Dent GA, Kohler M, Berchuk A, McLachlan JA, Boyd J: Mutations of the Ki-*ras* oncogene in endometrial carcinoma. Am J Obstet Gynecol 167:227–232, 1992.
25. Dunton CJ, Balsara G, McFarland M, Hernandez E: Uterine papillary serous carcinoma: A review. Obstet Gynecol Surv 46:97–102, 1991.
26. Gallion HH, van Nagell JR Jr, Powell DF, Donaldson ES, Higgins RV, Kryscio RJ, Pavlik EJ, Nelson K: Stage I serous papillary carcinoma of the endometrium. Cancer 63:2224–2228, 1989.
27. Sturgeon SR, Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD: Past and present physical activity and endometrial cancer risk. Br J Cancer 68:584–589, 1993.