Neoplasms of the Reproductive Tract: The Role of Hormone Exposure

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Abstract

Cancers of the reproductive system are a major source of morbidity and mortality among women worldwide. Because the uterus, ovaries, and cervix are hormonally responsive tissues, exposure to endogenous or exogenous sex steroids can profoundly affect the carcinogenic process. Animal models developed to date provide valuable but imperfect systems in which to study neoplasms of the reproductive tract. Nonhuman primate models share the unique primate-specific endometrial physiology of humans, but rarely develop neoplasms of the reproductive tract. Therefore a surrogate marker approach is required for the study of hormonally induced cancer risk in primates. Rodents provide practical models in which tumorigenesis can be assayed in a short time and, with appropriate interpretation, can be used for assessment of risk, prevention, and therapeutic strategies. In addition to the spontaneous strain-dependent incidence of female reproductive cancers, the classical chemical and hormonal carcinogenesis models, and the use of xenograft approaches, novel genetically modified animals provide unique insights into relevant molecular mechanisms. Caveats in the use of rodent models include anatomical differences from the human reproductive tract, the greater possibility of different metabolic responses to hormonal agents than humans, strain variations in tumor type and hormonal responsiveness, and unexpected tumor phenotypes in genetically modified animals. Reported nonmammalian models are limited primarily to the study of ovarian carcinogenesis. Recent progress in the understanding of cervical carcinogenesis is encouraging. Unmet needs in this area of research include models of early events in ovarian carcinogenesis and strongly predictive models of endometrial cancer risk. Nonhuman primates remain indispensable for the study of some aspects of reproductive pathophysiology, but the best understanding of carcinogenesis in the reproductive tract requires a broad approach using complementary human, nonhuman primate, and nonprimate studies.

Key Words: animal models; breast; cancer; cervix; endometrium; neoplasia; nonhuman primates; vagina

Hormone-dependent Reproductive Tract Neoplasms in Women

The most common site for neoplasms of the reproductive tract in women in the United States is the body of the uterus, followed by the ovary and the cervix (Jemal et al. 2003). On a worldwide basis, the most common gynecological neoplasm in women is cervical cancer, second only to breast cancer as the most common cancer of women (Ferlay et al. 2001). Neoplasms of the endometrium and ovarian surface epithelium are generally considered to be hormone dependent because reproductive factors or effects of sex steroids have been identified that alter the risk of their development, and because they express sex steroid receptors. The majority of endometrial cancers express estrogen receptor alpha, occur in association with estrogen exposure, and have a characteristic gene profile. Type I (estrogen-dependent) neoplasms tend to have mutations in DNA mismatch repair genes and the PTEN gene, whereas type II (estrogen-independent) neoplasms are more likely to overexpress mutated forms of the tumor suppressor gene p53 (Oehler et al. 2003).

In the ovary, epithelial cancers are the most aggressive and prevalent type of neoplasm, accounting for approximately 85% of ovarian neoplasms in women (Merino and Jaffe 1993); hormonal risk factors include androgen exposure and progesterone deficiency; expression of estrogen and progesterone receptors is common but inconsistent. Cervical carcinomas generally arise in association with particular human papilloma virus (HPV1) subtypes (types 16 and 18). These neoplasms appear to be promoted by hormonal exposure (Smith et al. 2003), but they generally do not express sex steroid receptors. Because of the high prevalence of these three specific neoplasms and the corresponding need for animal model development, this article focuses on epithelial neoplasms of the endometrium, ovarian surface, and cervix uteri.

Developmental Effects

Despite the recognized potential for hormonal agents to increase the incidence of hormone-dependent cancers, rela-
Hormones and Cancer Risk in Premenopausal Women

During the reproductive years, several risk factors have been identified for cancers of the reproductive tract. Obesity, hyperinsulinemia, hyperandrogenemia, and relative hyperestrogenism caused by anovulation contribute to increased endometrial cancer risk (Kaaks et al. 2002) and ovarian cancer risk (Kuper et al. 2002). Parity is protective against endometrial cancer (Terry et al. 1999). Ovarian dysfunction such as that caused by polycystic ovarian syndrome increases endometrial cancer risk in young women (McDonald et al. 1977; Solomon 1999). Parity is protective against ovarian cancer; androgen excess appears to increase ovarian cancer risk, whereas progestin exposure diminishes it (Risch 1998). The use of progestin-containing oral contraceptives is associated with a 25 to 50% lower relative risk of epithelial ovarian cancer (Riman et al. 2002). With respect to cervical carcinogenesis, the recognized contribution of hormones is primarily in those women developmentally exposed to DES. There may also be an adverse promoting effect of oral contraceptive use on papillomavirus-induced neoplasms (Smith et al. 2003), which may particularly relate to long-term progestin use (Moodley et al. 2003).

Hormones and Cancer Risk in Postmenopausal Women

Cancers of the endometrium occur primarily in older women (mean age ~70 yr) (Purdie and Green 2001) and are promoted by endogenous or exogenous estrogens. Estrogen treatment of postmenopausal women was recognized in the mid-1970s to be associated with endometrial hyperplasia and endometrial cancer; the most complete meta-analysis of estrogen and endometrial cancer risk indicates a doubling of endometrial cancer risk in “ever” users of unopposed estrogen replacement, with nearly a 10-fold risk occurring in women after prolonged use of several years (Grady et al. 1995). The estrogen-associated risk is obviated by concurrent progestin use (Grady et al. 1995). Other risk factors include age, obesity, diabetes, early menarche, late menopause, infertility, nulliparity, and tamoxifen use. Even the relatively low serum estradiol concentrations in postmenopausal women are associated with gradients of risk for endometrial cancer (Akhmedkhanov et al. 2001). The first selective estrogen receptor modulator (SERM) — tamoxifen — has been found to increase endometrial cancer risk (Fisher et al. 1998). SERMs developed subsequently have not been associated with increased endometrial cancer risk, most likely because the lack of uterotrophic effects has become an important screening criterion for SERMs (Goldstein and Nanavati 2002).

The effect of postmenopausal hormonal exposure on ovarian cancer risk is currently unclear (Gambacciani et al. 2003). A recent study of nearly 800 women with ovarian cancers, analyzed by subtype reported no overall effect of estrogen replacement therapy or hormone replacement therapy on ovarian cancer risk, but reported a significantly greater relative risk of endometrioid and mucinous forms of epithelial ovarian cancer in women taking unopposed estrogen replacement therapy (Purdie et al. 1999). Further evidence of heterogeneity in disease expression was found by Garner and colleagues, who found that a specific polymorphism (A2) in the estrogen-metabolizing enzyme CYP17 was associated with increased risk of epithelial ovarian cancer (Garner et al. 2002).

Cervical cancer in postmenopausal women is generally considered to be hormone independent, and cervical cancers do not usually express sex steroid receptors (Staebler et al. 2002). However, a randomized presurgical trial of women with cervical cancer discovered that estrogen treatment increased cellular proliferation in cervical tumors (Bhatucharya et al. 1997). In contrast to this observation, Megevand and colleagues found that postmenopausal status or progestin treatment was associated with an increased likelihood of incomplete excision of cervical neoplasms (Megevand et al. 1996).

Nonhuman Primate Models: Strengths and Limitations

Reproductive Physiology

Old World primates are unique among nonhuman species in having a similar endometrial physiology to that of humans. A physiologically and histologically similar, roughly monthly menstrual cycle has been documented for several macaque species (Attia 1998; Corner 1924; Ghosh et al. 1993; Okulicz et al. 1997), baboons (MacLennan and Wynn 1971), and the great apes (Graham 1973). Old World primates also undergo menopause, including cessation of ovarian cyclicity, cessation of menses, and persistent elevations in pituitary gonadotropins (Hodgen et al. 1977), although reproductive senescence occurs later in life relative to women (Graham 1979). Primate endometrial responses in general may not be adequately modeled by studies of other species such as rodents and domestic animals because those species do not have the primate-specific pattern of cyclic endometrial growth and menstrual shedding.
Spontaneous Incidence of Reproductive Neoplasms

Despite the physiological similarities between Old World primates and humans, relatively few neoplasms of the female reproductive tract have been documented in nonhuman primates, and the role of hormonal exposure is unknown in most of these cases. The literature includes numerous general reviews of tumor incidence in nonhuman primates (Beniashvilli 1989; Kent 1960; Lapin 1982; McClure 1973; Seibold and Wolf 1973). The largest published necropsy study of neoplasms in baboons, macaques, and African green monkeys found that of more than 13,700 necropsy examinations and 363 neoplasms diagnosed, only 25 involved the female reproductive tract (Lapin 1982). A subsequent review of the world literature encompassing all nonhuman primate species reported a total of 18 cases involving the uterus (primarily leiomyomas), nine cervical neoplasms, including polyps, and 13 ovarian neoplasms, only one of which was epithelial (Beniashvilli 1989). Aside from these collected reports, two endometrial adenocarcinomas have been reported, one in a rhesus monkey (Strozier et al. 1972) and the other in a Celebese black macaque (Shaw et al. 1989). Only a few epithelial ovarian neoplasms have been reported (Kraemer and Vera Cruz 1972).

In addition to published cases, uterine leiomyomas are anecdotally considered common in macaques, to the degree that cases are seldom published. This relatively low incidence of endometrial and ovarian neoplasms in the published literature must be considered a limitation of primate models for hormone-dependent neoplasms of women, although it should be remembered that a similarly small random sample of women would detect few neoplasms. For example, the incidence rate per 100,000 women is approximately 40 for endometrial cancer and 25 for ovarian cancer (Jemal et al. 2003), and the number of nonhuman primate necropsy examinations represented in all published reports is probably less than 20,000.

Although cervical cancers have seldom been reported, cervical dysplasias have been recognized for many years in macaques (DiGiacomo 1977; Hertig et al. 1983). In recent years, papillomaviruses have been identified in both benign papillomas and malignant epithelial neoplasms of the cervix and vagina of rhesus and cynomolgus macaques (Ostrow et al. 1990; Wood et al. 2003). Corresponding penile lesions in male animals have been identified, and there is molecular biological evidence for sexual transmission of the viruses (Ostrow et al. 1990; J.M.C., unpublished observations). Given the high prevalence of papillomavirus-associated cervical carcinomas in the human population, further exploration of this unique model is indicated.

Modeling Hormonal Carcinogenesis in Nonhuman Primates

Endometrial hyperplasia is readily induced in macaques by unopposed estrogen treatment (Figure 1), with correspond-
taken the approach of evaluating morphological responses of the reproductive tract and expression of the cell proliferation marker Ki76/MIB as a surrogate for this tumor-promoting effect in the reproductive tract. In general, hormonal treatments associated with increased cancer risk in women (such as estrogens) reveal increased endometrial proliferation, and those hormonal treatments that are protective (such as progestins) have caused reductions in proliferation (Cline et al. 2001). Furthermore, particular hormonal agents that produce a characteristic endometrial response in women (e.g., endometrial fibrosis and cystic change in the case of tamoxifen, or endometrial stromal hyperplasia and bleeding in the case of some progestins) also produce that response in macaques (Cline et al. 2001, 2002). The recent report of formation of tamoxifen adducts in macaques may shed some light on the controversy regarding this finding in women (Schild et al. 2003).

Although ovarian neoplasms are apparently uncommon in macaques, regulation of growth and apoptosis of the ovarian surface epithelium has been studied in an attempt to understand the role of hormonal treatment on ovarian carcinogenesis using this animal model. In vitro studies have indicated that high doses of estrogens and progestins can control epithelial proliferation (Wright et al. 2002). Rodriguez and colleagues documented a proapoptotic effect of long-term progestin treatment in macaques (Rodriguez et al. 1998) (Figure 2), with a corresponding induction of the inhibitory growth factor TGF-beta (Rodriguez et al. 2002). This model has the potential for use in a serial biopsy setting with additional surrogate markers (Brewer et al. 2001).

Attempts to produce cervical neoplasms similar to those produced by DES in women have produced some relevant results. Prenatal exposure of rhesus monkeys to DES resulted in vaginal adenosis and anatomical changes identical to those seen in women (Hendrickx et al. 1987), and similar changes were seen in Cebus monkeys (Johnson et al. 1981), but neoplasms were not seen in either case. In a separate attempt to produce cervical carcinomas, Kaminetzky and Swerdlov (1968) found that estrogen treatment promoted chemical carcinogenesis in the cervix of rhesus monkeys. Speculations on cervical epithelial dysplasias in wild-caught macaques included the possibility of estrogenic causation (Hertig et al. 1983), although the recently recognized role of papillomaviruses in cervical cancer leads away from this interpretation. Nevertheless, given the confounding relation between virus exposure and oral contraceptive use in premenopausal women, primate models may provide a necessary means of evaluating the potential for hormonal effects on virally induced cervical carcinogenesis. Although HPV-associated neoplasms lose expression of the estrogen and progesterone receptors (Staebler et al. 2002), these receptors are abundant in the normal cervical epithelium of macaques as in women; therefore the potential remains for hormonal influences on cervical carcinogenesis and tumor progression. An example of estrogen receptor loss in cervical neoplasia in macaques is shown in Figure 3.

Rodent Models

The reproductive physiology and anatomy of rodents differ substantially from that of primates, and the spectrum of neoplasms of the reproductive tract in rodents differs from those seen in humans. Some neoplasms of the reproductive tract lack precise equivalents in human gynecological pathology. Nevertheless, the relative ease of working with rodents makes them suitable for addressing issues in reproductive carcinogenesis that cannot be addressed in primates, and the potential for genetic manipulation of mice presents extraordinary opportunity for mechanistic studies of hor-

![Figure 2](https://academic.oup.com/ilarjournal/article-abstract/45/2/179/790436/figure2?download=true)

**Figure 2** Percentage of surface epithelial cells showing apoptosis induced by treatment with progestin-containing oral contraceptives. Terminal uridylyl nucleotide end labeling technique (TUNEL). * = different from controls and ethinyl-estradiol-treated animals at p <0.001; ** = different from controls at p = 0.01; and different from ethinyl-estradiol-treated animals at p = 0.01. Modified from Rodriguez GC, Walmer DK, Cline M, Krigman H, Lessey BA, Whitaker RS, Dodge R, Hughes CL. 1998. Effect of progestin on the ovarian epithelium of macaques: Cancer prevention through apoptosis? J Soc Gynecol Invest 5:271-276.

![Figure 3](https://academic.oup.com/ilarjournal/article-abstract/45/2/179/790436/figure3?download=true)

**Figure 3** Cervical intraepithelial neoplasia (CIN) grade 1 (left) and grade 3 (right). Immunohistochemical stain for estrogen receptors; hematoxylin counterstain. Note absence of estrogen receptor staining in the center of the CIN lesion on the right. Bar = 100 μm.
Rats

The prevalence of uterine and ovarian neoplasms in commonly used rat strains is well characterized. In Fischer and Sprague-Dawley rats, uterine fibromatous polyps are the most common uterine tumor (up to 40% of aged Fischer rats and 22% of Sprague-Dawley rats). Endometrial adenocarcinomas are the most common malignancy (up to 5% of aged Fischer rats and 1.4% of Sprague-Dawley rats), followed by uterine stromal sarcomas (Brown and Leininger 1992; Kaspareit and Rittinghausen 1999). Three rat strains have shown high incidence of endometrial cancer. The first report documented a 39% prevalence of endometrial adenocarcinomas in an outbred colony of Han/Wistar rats (Deerberg et al. 1981). These neoplasms were associated with hyperplastic lesions and progressed to metastatic disease involving the abdominal cavity and lung. Tumors occurred with even higher incidence in inbred BD II/Han rats from the same colony. These tumors were subsequently found to be hormone dependent, more common in nulliparous animals, and prevented by progestin treatment (Deerberg and Kaspareit 1987; Deerberg et al. 1995). These neoplasms have recently been shown to have amplification or overexpression of the myc (Karssen et al. 2001) and ErbB-2 (Helou et al. 2001) genes. A high incidence of endometrial tumors (adenocarcinomas, 35%; all proliferative lesions, 60%) is also seen in the Donryu rat, a Japanese strain. These rats have high levels of circulating estrogen, a high estrogen:progesterone ratio (5x that of Fisher rats), and irregular estrous cycles, and in this sense may model hormone-associated risk in women (Nagaoka et al. 1990). A third high-incidence strain is the Sabra hypertension-prone rat (Mor and Lutsky 1986); incidence increases with age, and tumors occur more often in virgin rats.

Tamoxifen-induced endometrial cancers have been reported in rats (Carthew et al. 2000); however, rats have a different metabolism of tamoxifen relative to humans, with rats having more abundant formation of DNA adducts and a unique hepatocarcinogenic response due to a lower rate of glucuronidation of reactive tamoxifen metabolites (White 2003). Sprague-Dawley rats are more sensitive to tamoxifen than Fisher 344 rats but are relatively less sensitive to exogenous estradiol. This relation has been proposed as a model for interindividual differences in human responses to tamoxifen (Bailey and Nephew 2002).

Ovarian cancers in rats are uncommon (~1% lifetime incidence) and are most often granulosa-cell tumors, with relatively few epithelial neoplasms. Several different strategies have been used to induce or transplant ovarian neoplasms in rats. Intraovarian injection of carcinogens such as DMBA or MNU is a reliable technique although it results in formation of primarily sex cord-stromal neoplasms, which are not the most common in women. However, a particularly interesting finding in this model is a recently reported promoting effect of the estrogenic chlorinated hydrocarbon tetrachlorodibenzoepin on the carcinogenic process (Davis et al. 2000). Another strategy for modeling ovarian epithelial neoplasms is the transplantation of ex vivo transformed surface epithelial cells into syngeneic rat hosts, which mimics the metastatic pattern of ovarian carcinoma in women. A spontaneously transformed line has been developed in Fischer rats (Rose et al. 1996) as well as an erb-B2-transformed line (Davies et al. 1998).

Cervical carcinogenesis is less often modeled in rats. Intrauterine injection of N-ethyl-N-nitro-N-nitosoguanidine has been used to induce endometrial and cervical carcinomas in F344 rats (Ogino et al. 1989).

Mice

Although cystic endometrial hyperplasias, endometritis, and squamous metaplasias of the uterus are common in aged female mice, neoplasms are relatively uncommon and highly strain dependent. The most common naturally occurring uterine tumors in mice are mesenchymal, consisting of stromal polyps and leiomysomas in B6C3F1 mice, and a variety of endometrial stromal tumors, including schwannomas, in BALB/c mice. Histiocytic sarcoma, a multicentric mesenchymal neoplasm common in mice, frequently affects the uterus (Davis et al. 1999). Despite this limitation, mice provide the best-characterized model of uterine epithelial neoplasia arising from developmental estrogen exposure. Administration of DES to outbred CD-1 neonatal mice results in a high incidence of uterine adenocarcinomas (90% by 18 mo). The development of these tumors can be prevented by ovariectomy before puberty, and they grow as allografts in nude mice only in the presence of estradiol, suggesting that estrogen is a necessary promoter in addition to the developmental effect (Newbold et al. 1990). Other combined chemical/hormonal models have been used to explore endometrial carcinogenesis. ICR mice given intravaginal methylthiosourea and estradiol-17B develop endometrial carcinomas within 25 weeks (Niwa et al. 1996).

The incidence of ovarian neoplasms in mice is also highly strain dependent. In the strain most commonly used for chronic toxicity studies, the B6C3F1 hybrid; ovarian cystadenomas and tubulostromal adenomas predominate (Davis et al. 1999), whereas in the FVB strain used in the generation of many transgenic lines, ovarian teratomas are more common (Mahler et al. 1996).

Transplantable Tumors in Mice

A variety of estrogen-dependent endometrial carcinoma cell lines have been xenotransplanted into nude mice, including Ishikawa cells, ECC-1, EnCa101, and other lines (Gong et al. 1994; Satyaswaroop 1993; Vollmer 2003). Some lines such as the EnCa 101 human endometrial carcinomas are
designed to model intraperitoneal implantation metastasis. In the EnCa line estrogen stimulation results in more rapid tumor growth and expression of the c-fos oncogene in the tumor cells (Sakakibara et al. 1992). This tumor cell line expresses aromatase and thus grows in male mice via conversion of testosterone to estradiol. It may provide an important model of androgenic risk factors in women (Legro et al. 2001).

In contrast, another estradiol-dependent xenografted human endometrial carcinoma has shown that continued estrogen stimulation in the rodent host causes tumor differentiation and maintains estrogen and progesterone receptors, but lack of estrogen results in fewer estrogen and progesterone receptors, loss of differentiation, and more rapid tumor growth (Horvath et al. 1991). Non-neoplastic human endometrial tissue has also been xenografted into nude mice, and this model may be valuable for studies of early changes in endometrial carcinogenesis (Zaino et al. 1985). A number of primary ovarian carcinoma xenografts have been established in nude mice (Elkas et al. 2002) and severe combined immunodeficiency (SCID) mice (Xu et al. 1999), and a spontaneously transformed syngeneic ovarian surface epithelial cell line has been established as a metastatic tumor model in C57BL/6 mice (Roby et al. 2000). Human cervical cancer xenografts have included HeLa cells and a variety of other lines; most appear to be estrogen independent. Xenografts of precancerous lesions have recently been established by Tewari and colleagues in SCID mice; this model retains estrogen responsiveness and may provide novel insights into cervical carcinogenesis (Tewari et al. 2000).

**Genetically Modified Mouse Models**

The two most common mutations in human endometrial cancers are those of the tumor suppressor genes p53 and PTEN. Mice lacking functional p53 and PTEN have been generated, and both lines are tumor prone. However, these mutations do not produce a tumor phenotype targeted to the endometrium; lymphomas and a variety of other neoplasms are instead the most common types of tumors seen (Donehower et al. 1992; Podosypinaia et al. 1999). Genetically modified mice expressing the SV40 large T antigen under control of the Mullerian Inhibiting Substance I promoter develop ovarian epithelial neoplasms, which disseminate by peritoneal implantation and produce ascites, thus mimicking the human disease (Connolly et al. 2003). Mice expressing large T under control of the inhibin-alpha promoter develop ovarian granulosa-cell neoplasms (Mikola et al. 2003). Papillomavirus-induced cervical carcinogenesis has been modeled by creation of transgenic mice expressing transforming proteins E6 and E7 from carcinogenic types of human papillomaviruses (types 16 and 18) under control of keratin promoters (Song et al. 1999, 2000). Of particular interest to the issue of hormonal effects on cervical carcinogenesis is the recent observation by Park and colleagues that estrogenic stimulation of HPV-18 transgenic mice promoted cervical carcinogenesis (Park et al. 2003).

**Hamsters**

Uterine adenocarcinoma is a common tumor of Chinese hamsters, occurring in 25% of aged females (Brownstein and Brooks 1980). Histologically, these tumors are papilliferous and induce a strong desmoplastic response. Uterine adenocarcinomas are uncommon in Syrian hamsters but can be induced by treatment of neonatal animals with DES followed by estrogen exposure later in life (Leavitt et al. 1981).

**Nonrodent Models**

**Other Mammalian Models**

**Rabbits**

Uterine adenocarcinoma is the most common tumor of aged female domestic rabbits; reported prevalences vary between 15 and 60%. The tan, French silver, Havana, and Dutch breeds are predisposed. Because rabbits are induced ovulators, they are in estrus much of the time. The resulting persistent estrogenic stimulus may be the underlying cause. Rabbits with chronic liver disease have elevated estrogens and an increased incidence of adenocarcinoma (Greene 1941). The tumors are often multiple. Histologically, they consist of irregular glandular elements in loose vascular/myxoid stroma, and they are estrogen and progesterone receptor positive. The tumors invade locally and also metastasize to the lungs. The onset of neoplasms coincides with senile endometrial atrophy, but focal hyperplasia precedes the formation of neoplasms. Endometrial adenocarcinomas can also be induced in rabbits by methylcholanthrene or estrogen administration. Progestins lower the incidence of induced tumors and may cause regression (Griffiths et al. 1975). Autologous transplantation and cell culture studies have been performed using this model (Elsinghorst et al. 1984); however, it currently appears that the use of this model has decreased and that rodent models are favored.

**Domestic Species**

Uterine epithelial neoplasms are rare in domestic species with the exception of the ox, and even in this species, lymphomas are the most common uterine neoplasm. Cystic endometrial hyperplasia is common in dogs and cats, but epithelial neoplasms are very rare (MacLachlan and Kennedy 2002). Ovarian epithelial neoplasms have been reported in several domestic species and most often in the dog, in which they appear to be the most common ovarian neoplasm and tend to be malignant (Patnaik and Greenlee 1987). In a particularly unusual study, human ovarian neoplasms were orthotopically transplanted into cyclosporin-
immunosuppressed sheep for studies of radiotherapy because smaller animal models did not provide adequate modeling of tissue mass for dosimetry (Turner et al. 1998). Cervical neoplasms in domestic species are rare. There is well-known association between bovine papillomavirus infection, fibropapillomas, and malignancies of the urinary and gastrointestinal tract, but the bovine virus has critical genetic differences from oncogenic papillomaviruses, and no clear role of hormonal exposure has been identified (Campo 1997).

Nonmammalian Models

Relatively few nonmammalian species are useful for modeling human female reproductive neoplasms, with the exception of a few instances of ovarian neoplasia. For example, the incidence of ovarian surface epithelial neoplasms is high in aged chickens (layer hens) and aged pigeons. This high incidence in chickens is markedly diminished by long-term treatment with medroxyprogesterone acetate, thus potentially providing a model for ovarian cancer prevention by progestins (Barnes et al. 2002; Rodriguez-Burford et al. 2001). In the remainder of the female reproductive tract, a few neoplasms have been reported, including adenocarcinomas of the proximal oviduct. Ovarian germ cell neoplasms of Drosophila melanogaster have been reported in association with mutation of a specific gene, ota (Bae et al. 1994). Bivalve mollusks in some geographic areas (Mya spp. in Maine and Mercenaria spp. in Florida) have a high incidence of ovarian neoplasms (40-60%), possibly as a result of exposure to environmental toxicants (Van Beneden 1997).

Unmet Needs and Future Directions

No animal model is perfectly predictive of human responses, and each has its strengths and limitations. Ovarian cancer models in rodents at present are suitable for the study of late stage disease and the development of therapeutic agents, but the study of ovarian cancer prevention relies on models that are phylogenetically distant from humans (chickens) or species that do not develop ovarian neoplasms often (primates). With respect to the endometrium, a highly predictive model for endometrial hyperplasia and endometrial cancer induced by hormonal agents is needed; the uterus of Old World primates is the closest anatomically and physiologically to the human uterus, but these animals may be relatively resistant to the carcinogenic/tumor-promoting effects of estrogens.

Rat models of endometrial cancer are similar in their estrogen dependence and progression to neoplasia within a practical period of time, but they may differ in critical pathways as a result of different uterine physiology. Transgenic mouse models have molecular genetic abnormalities in common with human neoplasms, such as PTEN mutations, but the relevance of the highly penetrant and multisystemic tumorigenic phenotypes in constructed mouse models can be questioned. Perhaps the most exciting recent progress has been made in the development or recognition of new ways to study papillomavirus-mediated cervical carcinogenesis, with the recent development of transgenic mouse models and the characterization of cervical carcinogenesis in monkeys.

References


