



# Mechanistic considerations for reduced endometrial cancer risk by smoking

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## Abstract

This review provides mechanistic explanations on why smoking reduces endometrial cancer risk with the primary focus on polycyclic aromatic hydrocarbons (PAHs). PAHs from cigarette smoke can activate aryl hydrocarbon receptor-mediated pathways. This leads to (i) increased levels of anticarcinogenic metabolites of estradiol, (ii) suppression of estrogen receptor (ER)-mediated actions, and (iii) induction of endometrial apoptosis. In addition, hydroxylated metabolites of PAHs may also evoke antitumor effects via the ER, specifically ER $\beta$ . The nuclear receptor expression profile in the human endometrium continuously changes throughout the menstrual cycle. In addition, endometrial apoptosis plays a fundamental role in the regulation of the menstrual cycle. The dynamic ER, progesterone receptor, and aryl hydrocarbon receptor expression together with the importance of apoptosis in the human endometrium likely explains the anticarcinogenic effect of PAHs from smoking on the endometrium as opposed to that on the mammary gland.

## Addresses

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**Current Opinion in Toxicology** 2019, 14:52–59

This review comes from a themed issue on **Mechanistic Toxicology**

Edited by **Martin Van Den Berg** and **Stephen Safe**

Available online 16 September 2019

For a complete overview see the [Issue](#) and the [Editorial](#)

<https://doi.org/10.1016/j.cotox.2019.09.002>

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## Keywords

Endometrial cancer, Smoking, PAHs, Aryl hydrocarbon receptor, Estrogen metabolism, Apoptosis.

## Introduction

Tobacco smoking is one of the major causes of cancer in a large number of tissues owing to the high levels of genotoxic polycyclic aromatic hydrocarbons (PAHs), among others, in cigarette smoke. Associations between

smoking and cancer of the lung, oral cavity, pharynx, larynx, and esophagus have been firmly established for both men and women [1]. In women, positive associations with smoking have been established for breast, cervix, and ovarian tumors [1]. Strikingly, the risk of endometrial cancer is lowered by smoking in postmenopausal women [2]. This reverse relationship between smoking and endometrial cancer is already known since the 1980s [3,4], yet so far, clear mechanistic explanations have not been discussed in detail.

Similar to breast and ovarian cancer, the role of sex steroid hormones in the oncogenesis of endometrial cancer is clearly established [5,6]. However, their role in the ontogeny of endometrial tumor formation appears dissimilar from that of those in the breast and ovary. Owing to the pronounced role of estrogens, many studies on endometrial cancer focused on the role of estrogen receptors (ERs) [7–9] and phase I and phase II metabolism of estrogens [10–12]. Especially, the metabolism of estrogens appears to play a role in the reduced endometrial cancer risk by smoking in contrast with increased breast and ovarian cancer risk. Moreover, increased endometrial apoptosis by PAHs seems extremely relevant in the protection against endometrial cancer in smoking women in particular because endometrial apoptosis is a fundamental process in the human endometrium in regulating timely shedding of the endometrium during the menstrual cycle. In this review, we address the mechanistic aspects of estrogen metabolism and apoptosis in endometrial tumor formation and the protective role of PAHs thereon.

## Smoking and mechanistic aspects in endometrial tumor formation Cytochrome P450-mediated metabolism of estrogens

A key step in the metabolism of estrogens involves CYP1A1, CYP1A2, and CYP1B1 enzymes. These cytochrome P450 enzymes are expressed in endometrial tissue and are responsible for the formation of hydroxylated metabolites of 17 $\beta$ -estradiol (E2) and estrone (E1) [12]. In addition, other P450 enzymes, such as CYP3A4, are involved in hydroxylation of estrogens. An extensive metabolic scheme of E2 and E1 has been described by Tsuchiya et al. [12]. Especially, the activity of CYP1B1 has raised significant toxicological interest owing to its role in producing genotoxic estrogen

metabolites. CYP1B1 metabolizes E1 and E2 to 4-hydroxylated metabolites (4-OHE1/2), which can be further converted to E2-3,4-(semi)quinone that can form depurinating DNA adducts, generating mutations that may lead to tumor formation [12–15]. Conversely, CYP1A1 and CYP1A2 convert estrogens into 2-hydroxylated metabolites that do not possess genotoxic properties. When further methylated by catechol-O-methyltransferase (COMT), the secondary metabolites of 2-hydroxylated estrogens (2OH-E1/2) actually exhibit tumor-inhibiting properties. CYP1 enzymes can easily be induced by many exogenous compounds, for example, via activation of the aryl hydrocarbon receptor (AhR). Therefore, these enzymes may play a significant role in induction of estrogen-related tumors such as those of the breast and ovary, but also in the endometrium, by exogenous compounds.

CYP1B1 is constitutively expressed in extrahepatic tissues. Relatively high CYP1B1 expression can be found in the human endometrium, yet its physiological role is still unclear. Several polymorphisms have been identified in CYP1B1 that influence its catalytic activity. For example, several inherited point mutations in the heme-binding regions of CYP1B1 can influence its catalytic activity and subsequent formation of the genotoxic 4OH-E1/2 [16]. These results indicate that within the human population, differences in genetic sensitivity may exist with respect to the formation of estrogen-dependent tumors due to genotoxic estrogen metabolites. This also applies to endometrial tumors, yet molecular epidemiological studies are unclear with respect to the role of CYP1B1 polymorphisms in tumor formation [7]. Furthermore, ample studies have demonstrated that the role of metabolism of estrogens is influenced not only by genetic predisposition [12,17,18] but also by lifestyle factors such as smoking [19,20]. One study reported that endometrial tumors have a higher expression of CYP1B1 than that of the healthy endometrium [12,21]. As PAHs can induce CYP1B1 expression via activation of the AhR, it seems reasonable to assume that smoking will cause induction of CYP1B1, leading to increased formation of genotoxic estrogen metabolites and subsequent increased incidence of endometrial tumors. However, epidemiological studies actually report the opposite. A study by Kim et al. [22] may shed some light on this apparent paradox. PAH-induced CYP1B1 activity coincided with activation of caspases and apoptosis in an endometrial tumor cell line RL95-2. However, it should be noted that one human study found contradicting results with a higher activity of CYP1B1 in healthy endometrial tissues than in tumors [23]. Therefore, more studies are needed to further confirm the role of PAHs in inducing CYP1B1 and apoptosis in endometrial cells via an AhR-mediated pathway.

From a toxicological point of view, CYP1A1 is equally important as CYP1B1 in PAH-related carcinogenesis as

both enzymes catalyze the conversion of PAHs into genotoxic PAH metabolites that can form DNA adducts [24–26]. As PAHs can induce both CYP1A1 and CYP1B1 expression, the question also arises if the ratio between genotoxic (4-OHE1/2) and anticarcinogenic (2-OHE1/2) estrogen metabolites may influence the risk of endometrial tumors. As previously described, CYP1A1-mediated estrogen metabolism in combination with COMT leads to anticarcinogenic methoxylated estrogen metabolites [13]. Support for a protective role of CYP1A1 in endometrial cancer comes from a study by Hirata et al. [27]. Here, it was observed that lower CYP1A1 activity due to m1 and m2 polymorphisms leads to reduced formation of 2OH-E2, which concurred with a higher risk of endometrial cancer [27]. Another study showed that polymorphisms of CYP1A1 and CYP1B1 could indeed influence the ratio between 2OH-E2 and 4OH-E2 [28]. This role of genetic factors in CYP1 genes and influence of the 2OH-E2:4OH-E2 ratio is further supported by a study that observed an association between a combination of four or five low-risk genotypes of CYP1A1, CYP1A2, and CYP1B1 with a decreased risk of endometrial cancer [29]. Although ethnic differences exist for polymorphisms in CYP1A1 and CYP1B1 [28], ethnicity-related genetic differences for endometrial cancer are not clear [30,31].

### Phase II metabolism

Several studies addressed a possible role of phase II enzymes in endometrial cancer. These include COMT, sulfotransferase (SULT), uridine diphosphoglucuronosyltransferase (UGT), and glutathione S-transferase (GST) activities and the role of polymorphisms. However, these have been studied less extensively than CYP1B1 and CYP1A. Overall, it appears that P450 enzymes play a more important role in the etiology of endometrial tumors than phase II enzymes [32].

Several studies addressed the role of COMT in endometrial cancer. One study did not find an association with smoking on COMT gene expression and the occurrence of endometrial cancer in humans [33]. In contrast, another study has provided some evidence that COMT could protect against endometrial cancer. In this study, knockdown of COMT activity in immortalized human endometrial glandular cells increased cell proliferation, reactive oxygen species, and microsatellite instability [10]. These results provide some support that COMT expression may provide differences in susceptibility for endometrial cancer. Moreover, this effect may be related to differences in the COMT isoform as it was also reported that S-COMT (soluble isoform) is elevated in endometrial tumors, whereas membrane-bound COMT is higher expressed in healthy tissue surrounding the tumor [23]. Thus, at present, there is no equivocal evidence that smoking provides a protective effect on endometrial cancer via COMT expression.

The protective role of UGTs has also been studied in relation to endometrial cancer [34]. Especially, UGT1A1 and UGT2B7 isoforms were found to have a protective role against the genotoxic effects of 4OH estrogens in nonmalignant human endometrium cells. In fact, an increase in the UGT2B7 level decreased the genotoxic activity of 4-OH estrogen metabolites in these cells [35]. Interestingly, UGT2B7 was found to be overexpressed in cancerous endometrial tissue [23]. Nevertheless, a large epidemiological study did not detect a significant modulating role of UGT polymorphism in endometrial cancer [36].

GSTs play an important role in the detoxification of quinones, including those of PAHs and estrogen metabolites. Yet GSTM1, GSTT1, and GSTP1 polymorphisms appear not to be associated with endometrial cancer risk [37]. However, in primary endometrial cancer cells, GSTP1 was found to be overexpressed [23]. Another study with human endometrial tissues suggested that GSTT1, but not GSTM1, copy number may be associated with increased endometrial cancer risk. These associations were not affected by smoking status [38].

In addition, the role of specific isoforms of SULTs in the etiology of endometrial cancer has been studied. Elevated gene expression levels of SULT2B1 have been found in endometrial cancer cells, whereas expression of SULT1E1 and SULT1A2 was similar with healthy endometrial tissue [23]. Another study identified a specific variant of SULT1A1 with the occurrence of endometrial cancer [27]. To our knowledge, there are no studies on the occurrence of endometrial cancer, smoking, and the role of SULTs.

### Steroid receptors

Recently, two reviews addressed the role of different (nuclear) steroid receptors in the etiology of endometrial cancer [9,39]. In this review, we specifically focus on the role of the AhR, ERs, and progesterone receptor (PR) in relation to the possibly protective role of smoking in endometrial cancer.

The AhR and its nuclear transport protein, aryl hydrocarbon nuclear translocator (ARNT), are commonly expressed in endometrial tissue [40]. As a result, endogenous and exogenous AhR agonists, such as PAHs, are capable of inducing both CYP1A1 and CYP1B1 in endometrial cells. As described previously, the formation of procarcinogenic or anticarcinogenic estrogen metabolites can occur via AhR-mediated pathways involving the induction of CYP1A1 and CYP1B1 [12]. Interestingly, the amount of AhR mRNA in endometrial cells was actually found to be lower in women who smoked than in nonsmokers [40]. Although this observation has to be confirmed, the mechanistic implications could be that a potential oncogenic role of estrogen metabolites is reduced owing to a simultaneous reduction in CYP1B1.

Moreover, it is well known that the AhR can (de)activate a large range of genes and physiological pathways that play a role in (anti)oncogenesis [41]. Therefore, it can be expected that any changes in AhR expression may also have an impact on other relevant (anti)tumorigenic pathways.

The gene–gene interactions between the AhR and ERs are another important aspect that may be relevant for reduced occurrence of endometrial cancer in smokers. It has been well documented that activation of the AhR can lead to cross talk with ERs at the transcriptional level with estrogen-dependent genes. This cross talk leads to downregulation of ER $\alpha$  and subsequent anti-estrogenic effects at the cellular level [42,43]. This genomic cross talk between the AhR and ER $\alpha$  is apparently a two-way interaction; as in endometrial cells, E2 was found to reduce the expression of CYP1A1 and CYP1B1 [44,45]. Especially, the E2-mediated decrease in CYP1B1 may be of interest for endometrial tumor formation as it would lead to a reduction in genotoxic 4OH estrogens. In view of the binding properties for the AhR of various individual PAHs that are formed during smoking, there are sufficient mechanistic arguments that support a role of the AhR in affecting endometrial cancer risk, with or without the interaction on estrogen-dependent genes [42]. *In vitro* studies with endometrial cell lines have indicated that PAHs, such as benzo( $\alpha$ )pyrene, can reduce the E2-induced cell proliferation via an AhR–ER $\alpha$  cross talk [46,47]. This observation provides a mechanistic explanation on why smoking reduces the risk of endometrial cancer. Further support for the antiestrogenic effects of PAHs was found in a study on ovariectomized rats. Here, it was observed that 3-methylcholantrene caused a — albeit modest — decrease in E2-induced uterus growth [48].

Multiple studies have shown that estrogens are a distinct risk factor for endometrial cancer. Here, ER $\alpha$  activation plays a significant role by stimulating cell proliferation, whereas progestagens counteract the estrogen-stimulated processes [49]. Recently, the specific role of estrogens in endometrial tumors and their genomic differences with that in breast cancer has already been discussed in an excellent review [9]. Although not studied directly in endometrial cells, PAHs that are present in cigarette smoke have been shown not to activate ERs in MCF-7 breast tumor cells. However, when metabolized to hydroxylated PAHs, the binding affinity for both ER $\alpha$  and ER $\beta$  increases, being merely one to two orders of magnitude lower than that of estradiol [50].

In contrast with ER $\alpha$ , ER $\beta$  is considered a tumor suppressor and has been shown to inhibit proliferation, invasion, and tumor formation in various tumors [51,52]. To what extent specifically ER $\beta$  plays an inhibitory role in endometrial tumors, similar as in breast and ovary tumors, needs to be clarified further [39,53]. In this respect, the decreased ER $\alpha$ :ER $\beta$  ratio in malignant endometrial

tissue compared with that in normal endometrial tissue is worth noting [54]. An *in vitro* study found that a number of PAHs can exert antiestrogenic activities via ER $\beta$  [55]. Thus, a possible anticarcinogenic role may originate from the antiestrogenic or antagonistic interactions of PAHs or their metabolites with the ER $\beta$ .

In contrast to estrogens, progesterone and its interaction with the PR inhibits the growth of endometrial tumor cells [56,57]. Consequently, progesterone can inhibit E2-induced cell proliferation of endometrial tumor cells and possibly hyperplasia [9]. This mechanism also applies to mammary (tumor) cells, but the ER and PR expression in the endometrium is far more dynamic and depends on the menstrual cycle phase [54]. Therefore, any change in ER and/or PR expression may have greater effects on the endometrium than on mammary tissue. In addition, progesterone has been shown to induce COMT in endometrial cells, an effect that could explain the protective effect of progesterone against endometrial cancer [10]. It should be noted that in breast cancer cells, the formation of 4OH-E2 by CYP1B1 also results in an increased rate of cell proliferation and expression of estrogen-inducible genes, such as the PR [58,59]. Progesterone can also downregulate the activity of nuclear factor- $\kappa$ B (NF- $\kappa$ B), the latter being associated with metalloproteinases that can stimulate invasiveness and metastasis [60]. Furthermore, a mouse study has shown that tobacco smoke could increase the levels of the PR in endometrial tissue, thus increasing the protective effect against initiating endometrial tumors [8].

Thus, the available information from the literature points toward a protective effect of tobacco smoke on endometrial cancer either via modulation of AhR-, ER-, and PR-mediated pathways that may involve modulation of CYP1B1 and proliferation.

### Endometrial apoptosis

Of particular interest is the simultaneous induction of AhR-mediated one of CYP1B1 by dimethylbenz(a) anthracene (DMBA) as well as apoptosis and caspase activities in RL95-2 endometrial cancer cells [22]. Apoptosis and cell proliferation are extremely important in the uterine endometrium. During the late secretory and menstrual phases, senescent cells are eliminated from the functional layer of the endometrium through apoptosis, which is then followed by proliferation of new cells from the basal layer during the proliferative phase of the following cycle [61]. Decreased apoptosis is associated with increased survival of ectopic endometrial cells and endometriosis [62].

With respect to endometrial apoptosis, the apoptotic markers Bcl-2 (apoptosis inhibitor) and Bax (apoptosis promoter) have been studied mostly. These proteins have an opposing effect on apoptosis, and the Bcl-2:Bax ratio is used to discriminate between benign endometrial

hyperplasia and carcinomas. Studies show that a low Bcl-2:Bax ratio is prevalent in low-grade endometrial carcinomas [60,63], but with increasing grade, an increase in this ratio has been found [64]. Some studies suggest that this change in the ratio is mainly attributed to under-expression of Bax [65]. It has also been found that Bcl-2 expression can be regulated via ER $\alpha$  and PR [66], which is especially relevant in hormone-dependent tissues. Estrogen and its interaction with ER $\alpha$  caused an increase in the Bcl-2 level, which leads to a reduction in apoptosis of endometrial stromal cells [67].

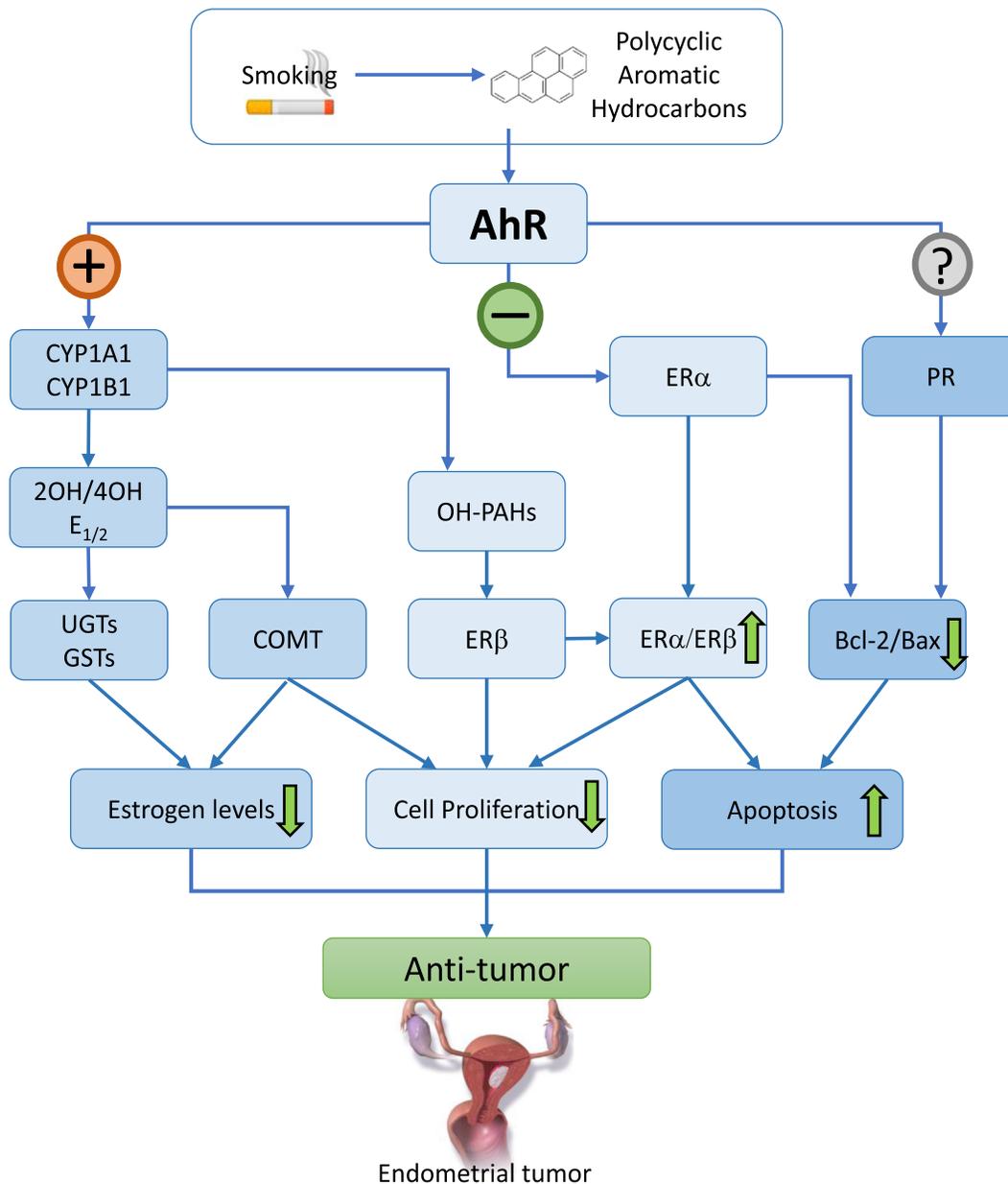
The changes in apoptotic markers in endometrial cancer are of particular interest from a toxicological point of view as it has been found that inducers of CYP1B1, for example, PAHs, are inducing apoptosis in endometrial cells at the same time [22]. No studies were found that specifically investigated the modulating role of smoking in Bax and/or Bcl-2 in endometrial cancer.

### Conclusions and summary

This review aimed to provide mechanistic explanations on why smoking reduces endometrial cancer risk, which is in strong contrast with many other types of cancer caused by smoking. While we focused on PAHs, we acknowledge that cigarette smoke contains hundreds of other chemicals as well that collectively can contribute to smoking-associated cancer.

Taken together, PAHs from cigarette smoke can lead to upregulation of AhR pathways in endometrial cells, subsequently leading to (i) increased levels of anticarcinogenic metabolites of estradiol, (ii) suppression of ER-mediated actions, and (iii) induction of endometrial apoptosis. In addition, PAHs or their hydroxylated metabolites may evoke antitumor effects via ER $\beta$ , which appears to be particularly relevant in endometrial tissue. These mechanisms are summarized in Figure 1. Clearly, these processes also play a role in other hormone-dependent tissues such as the mammary gland, but the particular protective or anticancer effect of smoking on the endometrium may lie on the physiology of this tissue. The human endometrium displays a dynamic nuclear receptor expression throughout the menstrual cycle, and especially, the relative expression of ERs, PR, and AhR may explain the differential carcinogenic effects of smoking on the mammary gland and endometrium. In addition, apoptosis and proliferation are fundamental processes in the endometrium in regulating the shedding of endometrial cells throughout the menstrual cycle, which is distinctly different from the mammary gland. This is not only relevant from a clinical point of view; the mechanisms described in this review may also aid in understanding of the role of anthropogenic exposures in the increasing rates of endometrial diseases.

Figure 1



**Aryl hydrocarbon receptor (AhR)-mediated pathways that may lead to reduced endometrial cancer risk by polycyclic aromatic hydrocarbons (PAHs) from smoking.** 2OH/4OH-E<sub>1/2</sub>, 2- and 4-hydroxylated estrogens; Bax, apoptosis promoter; Bcl-2, apoptosis inhibitor; COMT, catechol-O-methyltransferase; CYP1A1, cytochrome P450 1A1; CYP1B1, cytochrome P450 1B1; ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; GSTs, glutathione S-transferases; OH-PAHs, hydroxylated PAHs; PR, progesterone receptor; UGTs, uridine diphospho-glucuronosyltransferases.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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