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Cigarette Smoking and Estrogen-Related Cancer

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Abstract

Cigarette smoking is a known cause of many cancers, yet epidemiological studies have found protective associations with the risk of four “estrogen-related” malignancies: endometrial cancer, endometrioid and clear cell ovarian cancers, and thyroid cancer. This review considers epidemiological and biological aspects of these associations, focusing particularly on estrogen signaling, and contrasts them with those for breast cancer, another estrogen-related malignancy. The observational findings regarding the inverse associations are consistent and remain after adjustment for possible confounding factors. In general, women who smoke do not have lower circulating estrogen levels than non-smokers, eliminating one possible explanation for reduced risks of these malignancies. For endometrial and endometrioid ovarian cancer, the negative associations could plausibly be explained by interference with signaling through the estrogen receptor alpha. However, this is unlikely to explain the lower risks of thyroid and clear cell ovarian cancers. For thyroid cancer, an anti-inflammatory effect of nicotine and reduced TSH levels from smoking have been proposed explanations for the inverse association, but both lack convincing evidence. While the overall impact of cigarette smoking is overwhelmingly negative, protective associations such as those discussed here can provide potential clues to disease etiology, treatment and prevention.

Keywords

endometrial cancer; ovarian cancer; thyroid cancer; cigarette smoking; estrogens

Cigarette smoking is a well-known serious health hazard, increasing the incidence and mortality of a host of chronic diseases (1). It causes cancer at many sites, most prominently those with direct contact with cigarette smoke such as the oropharynx, larynx, and lung (2). Cigarette smoking is also associated with increased risks of cancer in some organs that lack direct smoke contact such as those in the urinary tract and pancreas (2). In contrast, smoking

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has been associated with a *reduced* risk of a few cancers in organs lacking smoke contact: endometrial cancer (3,4), endometrioid and clear cell ovarian cancer (5) and thyroid cancer (6). Is there reason to believe that these protective associations are real?

One thread connecting these malignancies is their relationship to sex: all endometrial and ovarian cancers and most thyroid cancers develop in women. Not surprisingly, these cancers are often thought to be "estrogen-related." Here, we summarize the associations of cigarette smoking and estrogens with these malignancies and consider possible explanations for reduced risks in smokers. We also consider another estrogen-related malignancy - breast cancer – for which smokers do not have a reduced risk.

Cancer of the endometrium

Cigarette smoking has a clear inverse association with risk of endometrial cancer. A combined analysis of data from cohort and case-control studies show that current smokers had a lower risk for all histological types investigated except the rare clear cell tumors (4). The association were seen in both case-control and cohort studies. For the most common histologies (those reported as endometriod, "type 1" or simply adenocarcinoma) there was a 35-40% reduction in risk. Odds ratios for former smokers were intermediate between those for current and never smokers. A meta-analysis showed that the smoking association was limited to post-menopausal women and may be stronger among those who used menopausal estrogens (3). In two cohort studies, the duration of premenopausal smoking was unrelated to risk, while the duration of smoking after menopause was inversely associated (7,8).

Cigarette smoking also has an impact on the non-neoplastic endometrium. In a cross-sectional analysis of a "representative sample of healthy postmenopausal women," the endometria of smokers were more atrophic than that of non-smokers (9). Two case-control analyses of women who underwent endometrial sampling reported that smokers have a lower risk of endometrial hyperplasia (10,11).

An important question is whether the apparent protective association of smoking with endometrial cancer is due to the smoking itself, or to other characteristics of smokers that confer protective effects. Of particular interest are factors associated with both smoking and estrogenic stimulation, as endometrial cancer risk is greatly increased by exposure to estrogens acting through the estrogen receptor α (ERα) (12,13) (Table 1). Large cohort studies document that pre-diagnostic circulating estrogen levels are strongly associated with endometrial cancer incidence in post-menopausal women (see e.g. (14-16)), and a meta-analysis documents high risk with use of unopposed menopausal estrogens (17). Collaborative analysis of case-control and cohort studies (4) as well as meta-analyses (18,19) document that in post-menopausal women high body mass index (BMI) is a strong risk factor, reflecting estrogens generated in adipose tissue by metabolism of adrenal androgens (20). In addition, there are several reproductive factors that have been associated with endometrial cancer. Collaborative analysis and meta-analyses document that early age at menarche, late age at menopause, and low parity/nulliparity are risk factors (4,21-23). These are thought to act through the greater cumulative estrogenic stimulation generated by

the larger number of normal menstrual cycles experienced by women with these risk factors (24).

Several of these risk factors are also associated with cigarette smoking, raising the possibility that they could confound the smoking/endometrial cancer association. Meta-analyses show that current smokers have an earlier menopause than non-smokers (25,26) and the adverse effects of smoking on fertility and fecundity are well documented (2,27). Cross-sectional population surveys show that current smokers have a lower body weight than never or former smokers (see, for example (28-31)). However, the protective endometrial cancer associations described above are seen after adjustment for these factors, and have been reported in studies of various designs conducted in a variety of populations. Given the strength of this evidence, the associations do not appear to be due to chance, bias, or confounding.

Cancers of the ovary

Although cigarette smoking is not associated with the overall risk of epithelial ovarian cancer (5), this is a heterogeneous malignancy, comprising different phenotypes with distinct molecular and clinical characteristics (32). Only mucinous cancers are derived from ovarian tissue itself. Serous tumors originate in the fallopian tubes, and endometrioid and clear cell ovarian cancers are thought to be derived from the endometrium, probably through retrograde menstruation. Recent combined analyses of individual level data from case-control and cohort studies have provided detailed risk factor data for ovarian cancer according to tumor histology. Endometrioid ovarian cancer has many of the same estrogenic risk factors as endometrial cancer: increasing risk with use of unopposed menopausal estrogens (33), lower parity and late age at menopause (34) (Table 1). Higher BMI has also been associated with increased risks of endometrioid ovarian cancer in collaborative analyses and meta-analyses (34-36), though the association in postmenopausal women specifically is less clear in the few studies that have investigated it (37,38). Clear cell cancers share some estrogenic risk factors, but there is at most a weak association with BMI (34-36) (even among postmenopausal women (38)) and no association or a *reduced* risk with use of unopposed estrogens (Table 1) (33,39). ERα is commonly expressed in endometrioid ovarian cancers, but not in clear cell tumors (40,41).

Collaborative analysis of case-control (5,42) and cohort studies (5) show that the associations of ovarian cancer with cigarette smoking differ according to the histology of the tumors. Smoking is not associated with serous ovarian cancer, and confers an increased risk of mucinous tumors. In contrast, the relationship of smoking with risk of endometrioid ovarian cancer resembles that for smoking and endometrial cancer. There is a reduction in risk of about 20% among current smokers that is attenuated in former smokers, and the associations are not confounded by factors such as BMI, use of hormone replacement therapy, oral contraceptive use, or reproductive history. There are no interactions of smoking status with BMI, alcohol use, parity, oral contraceptive use, menopausal hormone use, or family history of ovarian or breast cancer. Unlike endometrial cancer, the association with current smoking appears to be similar in pre- and post-menopausal women. Population-based case-control studies and cohort studies showed similar findings. There are less data

available regarding smoking and clear cell ovarian cancer, but the inverse association for this malignancy is similar to that for endometrioid ovarian cancer.

Cancer of the Thyroid

The association of smoking with risk of thyroid cancer is also broadly similar to that for endometrial cancer: a meta-analysis (6) and a pooled analysis of cohort studies (43) found that current smokers (but not former smokers) have about a 25-30% lower risk than never smokers. This pattern is evident in women as well as in men (6). A combined analysis of cohort studies and the large Women's Health Initiative cohort study document that the association remains after adjustment for alcohol intake and BMI (and for reproductive factors in women) (43,44). In addition, the combined cohort analyses reported that there is no apparent interaction of current smoking with age, sex, education, or BMI (43). The reduction in risk among current smokers is seen in both medullary and papillary thyroid cancer, though reductions in risk may be slightly larger for tumors with papillary histology (which comprise about 90% of thyroid cancers overall) (6,43),

An estrogen dependence of thyroid cancer is clearly evident in rodent models and cell culture studies (45,46), and ERα is expressed in this malignancy (46). Nonetheless, the epidemiological characteristics of an estrogen dependence are relatively weak (Table 1). Though incidence is higher among women than among men, mortality rates in the US are very similar (47). Meta-analysis and a pooled analysis of case-control studies show an *increased* risk among parous versus nulliparous women (though without a dose-response trend) (48,49) and there is a suggested *increased* risk with later age of menarche (48,50). Whether a late age of menopause is associated with an increased risk is not clear: a meta-analysis of cohort studies and the pooled case-control analysis (48,51) suggest that it is not, though two meta-analyses suggest that it is (52,53). In any case, the pooled analysis of case-control studies (48) and the Women's Health Initiative cohort (54) show that women who have a surgical menopause have an *increased* risk. Meta-analysis (55) makes clear that thyroid cancer risk is positively associated with BMI in women. Studies that have assessed this in older or post-menopausal women in particular are generally consistent with a modest in increase in risk (56-62). Case-control (63) and cohort analyses (58,64-66) have not reported clear associations with unopposed menopausal estrogen therapy. Thus – at least epidemiologically -- thyroid cancer does not display the characteristics of an estrogen-sensitive malignancy.

A complicating factor in thyroid cancer epidemiology is the overdiagnosis of subclinical lesions, which has led to a dramatic increase in recorded incidence over the past several decades (47). Thus, differential surveillance might play a role in the higher incidence in women. However, it is unlikely to underlie the inverse association with smoking: the utilization of outpatient care by current smokers has been variously observed to be less than (67), greater than (68), or about the same as that of non-smokers (69).

Breast Cancer

Collaborative analysis of case-control and cohort studies of breast cancer show that the hormone receptor positive phenotypes share much of the estrogenic risk factor profile seen in endometrial cancer: increased risks associated with early menarche, late menopause, low parity, and high post-menopausal BMI (70-73) (Table 1). However, the effect of unopposed menopausal estrogens is not clear: observational studies have found users to have modestly increased risk (74), but the Women's Health Initiative clinical trial found reduced risks (75) (Table 1).

In contrast to the other cancers considered here, cigarette smoking is not associated with a reduced risk of breast cancer. A pooled analysis of 14 cohort studies reported a small (7%) overall increase in risk among current smokers. There was a statistically significant interaction with alcohol drinking, with no increased risk among women who did not currently drink. Even the most estrogen-sensitive phenotypes, those that are ER positive or that have a luminal expression profile, do not display an inverse association with smoking: a pooled analysis of cohort studies reported a small increase in risk for ER positive breast cancer (76) and similar findings were reported for luminal phenotypes in population-based case-control studies (76-78).

An interesting detail is that the relationship between smoking and breast cancer seems to differ depending on the ages when the smoking occurs. A pooled analysis of cohort studies documents that smoking initiation early in life has been consistently associated with a small increase in risk, particularly among women who started smoking before their first term birth (76). On the other hand, three large cohort studies found that the duration of post-menopausal smoking was inversely associated with risk while that for premenopausal smoking tended to increase risk (79-81). This mirrors the pattern observed for endometrial cancer, in which post-menopausal smoking – but not premenopausal smoking - is associated with reduced risks (7,8).

Although smoking is not inversely associated with breast cancer risk, women who currently smoke have a lower radiographic breast density than former or never smokers (see, for example (82,83)). A recent comprehensive study from a health insurance plan included over 23,0000 women and provides the most precise estimates (83). The lower breast density was seen in both premenopausal and postmenopausal current smokers, and was largely due to an increase in the non-dense breast area rather than a reduction in the dense areas.

Cigarette Smoking and Circulating Estrogen Levels

One explanation for the inverse association of three estrogen-related cancers with cigarette smoking would be that smoking lowers concentrations of circulating estrogens. However, serum estrogen levels are *not* lower among women who smoke. Among premenopausal women, circulating estradiol has variously been found to be slightly higher in current smokers than in non-smokers (*e.g.* (84)) or similar (*e.g.* (85)). There are more data for post-menopausal women, conveniently summarized in a collaborative analysis. For them as well, current smokers have similar or slightly *higher* circulating estradiol and estrone than their

non-smoking peers (86). Estimated (86) and measured (87) free estradiol levels show the same pattern. Clearly, differences in circulating estrogen levels cannot explain an inverse association of smoking with the estrogen-related cancers being considered here.

Post-menopausal women who both smoke and use oral estrogens do have lower serum estrogen levels than non-smokers, exhibiting as much as 50% lower circulating estradiol and estrone (88,89). This is due to hepatic first pass metabolism of the oral hormones induced by constituents of cigarette smoke, as discussed below. No differences are seen in women using parenteral (88) or percutaneous (89) estrogens. The lower achieved estrogen levels in women who smoke while using oral estrogens result in smaller improvements in bone mineral density and serum lipoprotein levels than for non-smoking postmenopausal women (89). There is as well a reduced estrogen-induced trophic effect on the endometrium (9). These findings could contribute to the reduced risk of estrogen-related cancers among women who actively smoke while taking menopausal estrogens. Nonetheless, in a large cohort study (90) and a hospital-based case-control study (90) the reduced risk of endometrial cancer among smokers was still found among those who used menopausal hormone therapy. (This issue has not been specifically investigated for endometrioid and clear cell ovarian cancers or thyroid cancer).

Cigarette Smoking, Nicotine and Aromatase

How could cigarette smoking impede estrogen-related carcinogenesis without reducing circulating estrogen levels? One possibility is through the reduction of local synthesis of estrogens in the organs at cancer risk (Table 2). In peripheral tissues, cytochrome P450-19 (CYP450-19); aromatase) metabolizes the androgens androstenedione and testosterone to estrone and estradiol, respectively (91). This is important for local estrogen signaling: in the breast and ovary, for example, tissue levels of estrogens are an order of magnitude higher than would be predicted from circulating levels (92). The enzyme is present in the proliferative endometrium, the ovary and the thyroid, and is expressed in breast, endometrial and thyroid cancers as well as in endometriosis and endometrioid ovarian cancer (93-96). Nicotine and other constituents of tobacco and tobacco smoke inhibit the enzyme *in-vitro* (97,98), and smokers have lower expression in the brain (99) and in the placentas of pregnant women at term (100). Smoking may also inhibit aromatase in breast cancer tissue (101). The effect of smoking on aromatase in endometrial, ovarian and thyroid cancers has not been investigated, but important effects on endometrial cancer are unlikely since aromatase expression is low in that malignancy (102).

In general, nicotine is not thought to have anti-neoplastic properties (103), though it can have anti-inflammatory effects, due at least in part to stimulation of α7 cholinergic receptors on immune cells (104). This can suppress macrophage secretion of inflammatory mediators such as IL-1β, TNFα, and IL-6; inhibit dendritic cell activity; and modulate T-cell differentiation (105,106). Observed consequences are an inhibition of Th1 and Th17 inflammation, and an increase in T-regulatory cell activity (107). Consistent with these effects, transdermal nicotine can reduce skin inflammation caused by UV light exposure (108) and induce remission in ulcerative colitis (109). Current smoking has been inversely associated with some inflammatory disorders: ulcerative colitis (110), pemphigus (111), and

sarcoidosis (112), for example. But it certainly does not have a general anti-inflammatory impact, as it is positively associated with inflammatory diseases such as rheumatoid arthritis (113), systemic lupus erythematosus (114), and Crohn's disease (110).

Inflammation appears to promote endometrial carcinogenesis independently of estrogens (115,116) so any anti-inflammatory effect of smoking could contribute to an anti-neoplastic impact on endometrial cancer. Nicotine's anti-inflammatory effect could also be relevant for ovarian cancers derived from endometriotic tissue since endometriosis is clearly an inflammatory disorder and nicotine has been found to ameliorate it in experimental models (Table 2) (117). But translation of this finding to human ovarian cancer is not straightforward: some studies have reported lower endometriosis prevalence among women who smoke, but – as summarized in a meta-analysis -- overall there does not appear to be a substantial association (118).

Cigarette Smoking, Polycyclic Aromatic Hydrocarbons, and the Aryl Hydrocarbon Receptor (AhR)

In addition to nicotine, cigarette smoke contains close to 4000 chemicals, including tobacco-specific nitrosamines and over 500 polycyclic aromatic hydrocarbons (PAHs). Many of these are well known carcinogens (1). However, PAHs and other compounds in cigarette smoke have other important biological effects as ligands for the aryl hydrocarbon receptor (AhR) (119). In its classical function, the liganded AhR, together with its partner protein, the AhR nuclear translocator (ARNT), binds to specific binding sites in the promotor regions of target genes (the xenobiotic responsive element (XRE) containing a core GCTGC sequence). This initiates transcription of a broad spectrum of well-characterized genes and activation of pathways such as phase I and II xenobiotic metabolism (120,121). Cigarette smoke is rich in AhR ligands, many formed during the incomplete combustion of tobacco (119). The AhR receptor plays a role both in maintaining cellular homeostasis and in pathophysiology, and is widely expressed in malignancies, including all those discussed here (122,123).

The importance of AhR ligands in estrogen-sensitive tissues extends beyond metabolism of carcinogens, since there is well-established cross-talk between AhR and ERα signaling (Table 2, Figure). Some PAHs – or their metabolites – can act *in vitro* as weak selective estrogen receptor modulators (SERMs) (124), activating ERα and ERβ with a potency many orders of magnitude weaker than that of estradiol. These effects vary across tissues depending on expression levels of the receptors and cell context (124,125). But in general, AhR ligands, including 2,3,7,8-tetrachlorodibenzodioxin (TCDD, "dioxin") and PAHs such as benzo[a]pyrene, benz[a]anthracene, and methylcholanthrene (3-MC) exhibit clear anti-estrogenic effects. In breast cancer cell lines that express ERα, they counter the effects of estradiol on proliferation, epidermal growth factor receptor (EGFR) levels and cyclin D expression, and downregulate ERα expression (126,127). Similar anti-estrogenic effects of AhR ligands are seen in endometrial cancer cell lines (128-130).

The anti-estrogenic cross talk occurs through several pathways (Figure) (127,131). AhR signaling induces CYP1A1, CYP1A2, and CYP1B1, enzymes that metabolize the major estrogens estrone and estradiol to less active metabolites, thus reducing the local

concentration of the most potent ERα agonists (132). CYP1A1 is responsible for the first pass metabolism of oral estrogens in the liver. Liganded AhR also promotes proteasomal degradation of ERα and competes with ERα for shared nuclear cofactors and coactivators. Further, AhR signaling has the potential to directly interfere with the transcription of ERα-regulated genes: binding of the liganded AhR complex to an inhibitory XRE in some of these genes disrupts the interactions of coactivators needed for ERα transcription. Finally, induction of a protein that inhibits estrogen signaling has also been observed (though not identified).

In-vivo, an anti-estrogenic impact of AhR ligands is evident. In ovariectomized rats, 3-MC attenuated expression of the majority of estradiol-induced genes in the mammary gland and endometrium, and reduced the development of mammary terminal end buds (133,134). AhR ligands also inhibited expression of the ERα and the progesterone receptor in the uteri of estradiol-treated rats (135-137) and reduced estrogen-induced rodent uterine growth (136,138,139). In a 2-year study of dioxin in rats, exposed animals had a reduced incidence of “uterine changes,” including endometrial hyperplasia, cyst formation and adenomatous polyps (140). In another study, an endogenous AhR agonist, 2-(1′H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE), suppressed endometrial cancer xenografts (130).

Given these observations, it is not surprising that cigarette smoke itself has shown anti-neoplastic effects in preclinical models of estrogen-related malignancies. Despite the fact that constituents of cigarette smoke, including some PAHs, are recognized mammary carcinogens (141), cigarette smoke reduces mammary tumor incidence in rats (142,143) (as does nicotine-dosed feeding with smokeless tobacco (144)). In one long term study, rats chronically exposed to cigarette smoke had fewer uterine and ovarian tumors than those unexposed (142).

Cigarette Smoking, Inflammation, Cell Proliferation and Thyroid Cancer

Smoking is associated with several thyroid disorders, including an increased prevalence of goiter in iodine-deficient areas, and an increased risk of Graves hyperthyroidism (145,146). However, these findings would not explain an apparent protective effect of smoking on thyroid cancer. An anti-estrogenic effect of cigarette smoking has been proposed as an explanation, but the lack of epidemiological markers of estrogen responsiveness for thyroid cancer etiology reduces the plausibility of this argument.

Chronic inflammation has a well-recognized carcinogenic impact (147) that may be relevant for thyroid cancer. Autoimmune (Hashimoto’s) thyroiditis is a chronic inflammation of the gland that has been associated with thyroid cancer in a series of cross-sectional studies (see, for example (148-150)) and may also be inversely associated with smoking. In population surveys in Western countries (151,152), current smokers have a lower prevalence of the autoantibodies associated with autoimmune thyroiditis (151,152), though this association may depend on iodine status (152,153) and findings in Asia have been mixed (see e.g. (153-156)). Data regarding the association of smoking with thyroiditis itself are conflicting. An early meta-analysis of two studies found increased risks in smokers (145). Subsequent

investigations reported reduced risks (157,158) or null findings (for example, (159-161)). Interpretation of all these studies is hampered by differences in criteria for autoimmune thyroiditis, and the fact that many of the investigations suffer from an ill-defined study base, investigation of prevalent cases, small sample sizes, and/or unadjusted analyses. Furthermore, evidence for an association between thyroiditis and thyroid cancer is largely derived from cross-sectional studies that were prone to selection biases in which high risk patients were more likely to be confirmed as cancer cases (148,162). Given these uncertainties, an anti-inflammatory effect of smoking is also not a convincing explanation for the inverse association of smoking with thyroid cancer.

Another proposed explanation for a reduced risk of thyroid cancer in smokers is the lower levels of thyroid stimulating hormone (TSH, thyrotrophin) that has been documented in current smokers in population surveys ((152,156,163,164)). TSH is a growth factor for thyrocytes, and suppression of TSH secretion is used in the treatment of thyroid cancer (165). In cross-sectional studies of patients investigated for thyroid disease, those with thyroid cancer have higher TSH levels than those without (166), but in nested cohort analyses pre-diagnostic levels are not higher in future cases than in controls (167,168) and in a large Korean cohort study, adjustment for serum TSH only slightly attenuated the observed smoking association (169). TSH-supported proliferation may be needed for the progression of transformed cells, but TSH stimulation alone is not thought to lead to thyroid carcinogenesis (170,171). Thus, whether lower TSH levels explain the reduced thyroid cancer risk in smokers is uncertain.

Conclusions

The inverse associations between cigarette smoking and risk of endometrial cancer, endometrioid and clear cell ovarian cancers and thyroid cancer are reasonably well-documented. Studies of various designs in different populations have reported the findings, and confounding variables or obvious study biases do not readily explain the associations. The epidemiology is consistent with causal associations. In contrast, another estrogen-related cancer, breast cancer, does not display similar smoking associations.

Although women who smoke cigarettes do not have lower circulating estrogen levels than non-smokers, the hormonal milieu within a tissue is likely to be more relevant for estrogen-related carcinogenesis. Inhibition of aromatase and the anti-estrogenic AhR effects detailed above clearly have the potential to interfere with local effects of estrogens. For endometrial cancer, this AhR interference with estrogen signaling is a plausible explanation for a causal protective effect of smoking. Inhibition of aromatase and consequent interference with local estrogen production seems less relevant, given the low aromatase expression in that malignancy, but a possible anti-inflammatory effect of smoking could support an anti-neoplastic effect (Table 2).

Inhibition of aromatase and AhR interference with estrogen signaling both seem relevant as explanations for the reduced risk of endometrioid ovarian cancer in smokers. But for clear cell ovarian cancer, the lack of expression of ERα and the weaker epidemiological suggestions of an estrogen dependence make estrogen-related mechanisms much less

compelling (Table 2). The possible anti-inflammatory effects of smoking could theoretically contribute to an anti-neoplastic effect of both endometrioid and clear cell ovarian cancers, but the lack of a clear association of smoking with endometriosis renders this uncertain.

Proposed explanations for the inverse association of smoking with risk of thyroid cancer are also unsatisfactory (Table 2). Since the epidemiology of this malignancy does not suggest a marked estrogen dependence, an anti-estrogenic effect of smoking is not a strong candidate. An anti-inflammatory impact of nicotine on thyroid cancer seems uncertain in light of the inconsistent data regarding the associations of smoking with thyroiditis and thyroiditis with thyroid cancer. Cigarette smoking does lower TSH levels, but it is not clear if that would be sufficient to lower risk of thyroid cancer. In summary, none of the proposed mechanisms for a protective effect of smoking on thyroid cancer risk are supported by compelling evidence (Table 2).

In contrast to the other estrogen-related cancers considered here, ER positive breast cancer is not inversely associated with cigarette smoking. Nonetheless, there are indications that post-menopausal smoking may temper any increased risks associated with premenopausal exposure. Together with the conflicting signals from preclinical studies, these findings suggest that smoking could have counterbalancing effects on breast carcinogenesis: a direct carcinogenic impact and a mitigating postmenopausal anti-estrogenic effect.

It is conceivable that cigarette smoking could impede carcinogenesis through pathways other than interference with estrogen signaling, hormonal regulation, or inflammation. The AhR is a “promiscuous” receptor that can respond to a wide variety of environmental (and endogenous) compounds drawn from many classes of substances (172). Recent research has shown that the AhR is involved in a range of biological processes relevant to carcinogenesis: cell cycle progression, cell adhesion, proliferation, and immune response, for example (173,174). Often this enhances carcinogenesis, but sometimes it can be anti-neoplastic (175,176). The extent to which these mechanisms explain the inverse associations of cigarette smoking with the cancers considered here have not been studied in any detail.

This reinforces an important point, that the effects of various AhR ligands and other constituents of cigarette smoke can differ. Moreover, AhR/ERα crosstalk is known to be context-dependent, varying across tissues with the expression of the AhR, ERα, ERβ, coactivators and suppressors of these receptors, and the various enzymes induced by the AhR (122). The fact that ERβ signaling often counteracts the effects of ERα (177) adds another element of complexity. ERβ is expressed in all the cancers discussed here (46,177,178), and may be particularly important for endometrioid and clear cell ovarian cancer because of its role in supporting the progression of endometriosis, which can evolve into these malignancies (94,179).

High BMI is a risk factor for endometrial cancer, endometrioid and clear cell ovarian cancers and thyroid cancer, but the impact of smoking on these malignancies cannot be interpreted as an “anti-obesity” effect of some sort. As noted above, current smokers do tend to have a lower BMI than non-smokers. But they also tend to have an abdominal distribution of adipose tissue, as reflected in a higher waist-to-hip ratio (180,181). This confers many of

the adverse consequences of high BMI itself – including increased risks of endometrial, postmenopausal breast and thyroid cancers (55,182); an increased risk of diabetes (183); and decreased circulating adiponectin levels (184).

Although there are plausible mechanisms to explain smoking's effect on endometrial cancer and endometrioid ovarian cancer, additional research will be required to more fully understand the inverse associations of smoking with clear cell ovarian cancer and thyroid cancer. Understanding what factors lead endometriosis to predispose to clear cell versus endometrioid ovarian cancer, with rather different estrogen associations, would contribute to the understanding of smoking's association with the former. Clarification of the associations of thyroiditis with smoking on the one hand and thyroiditis with thyroid cancer on the other is needed to understand the role of inflammation in thyroid carcinogenesis and the impact of smoking on thyroid cancer incidence.

Whatever the possible beneficial effects of smoking described here, the overall impact of cigarettes on health is undeniably extremely negative. The value of the unexpected protective associations discussed here is that they can provide clues to disease etiology, treatment and prevention, as has been the case for smoking's associations with ulcerative colitis and Parkinson's disease (185). The fact that smoking appears to exert an anti-estrogenic effect through AhR signaling suggests that this pathway would be a productive avenue for research regarding prevention or treatment for estrogen-related malignancies. Indeed, use of selective AhR ligands for treatment of breast cancer, and perhaps other malignancies, is an active line of research (122) and the AhR-active drug aminoflavone (186,187) has been in clinical trials for treatment of breast and other cancers.

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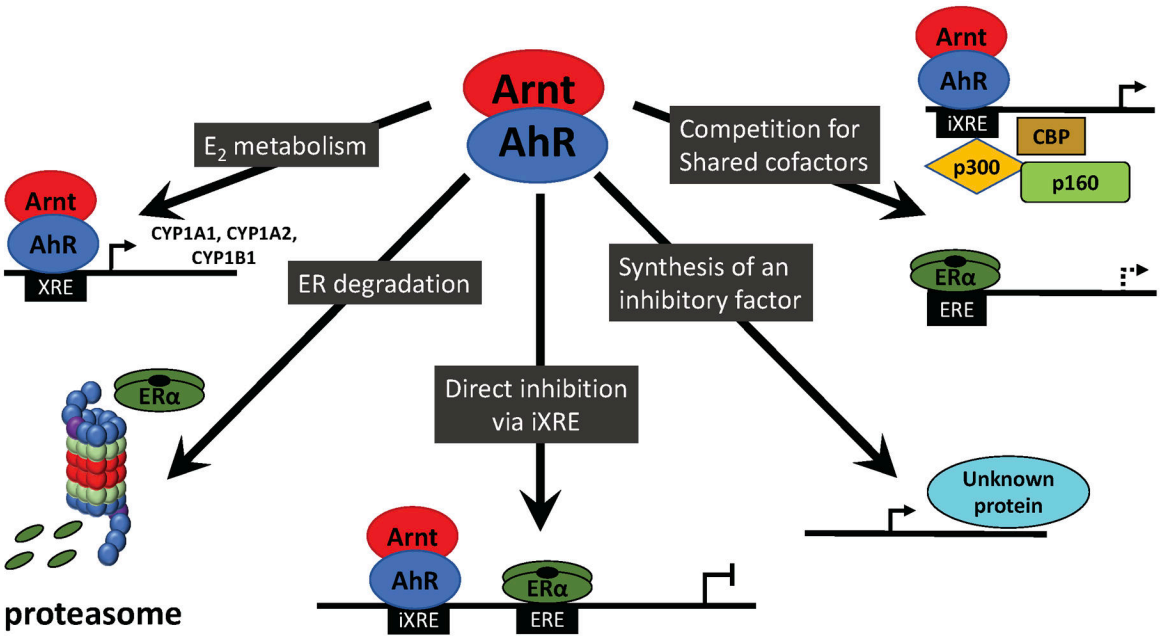

Figure 1.

Possible Mechanisms of AhR:ER crosstalk

Arnt, Aryl hydrocarbon nuclear translator; AhR, Aryl hydrocarbon receptor; XRE xenobiotic response element; iXRE incomplete xenobiotic response element; EREh estrogen response element; ERα, estrogen receptor α

Table 1.

Estrogen-related associations of endometrial cancer, endometrioid and clear cell ovarian cancers, breast cancer and thyroid cancer

	Endometrial cancer	Endometrioid ovarian cancer	Clear cell ovarian cancer	Breast cancer	Thyroid Cancer
Unopposed exogenous estrogen	↑↑ (17)	↑ (33)	0 or ↓ (33,39)	↑? (74,75)	0? (58,63-66)
Age at menopause	↑ (22)	↑ (34)	↑ (34)	↑ (70)	? (48,51-53)
Age at menarche	↓ (4,23)	0 (34)	↓ (34)	↓ (70)	↑? (48,50)
Parity	↓ (4,21)	↓ (34)	↓ (34)	↓ (72,73)	↑ (48,49)
Post-menopausal BMI	↑ (4,18,19)	↑(34-36)	0? (34-36)	↑ (71)	↑? (56-62)

↑↑ greatly increased risk; ↑ increased risk; 0 no association; ↓ decreased risk; ? unclear; 0? Suggestion of no association; ↑? Suggestion of increased risk

Table 2.

Possible Mechanisms Underlying Reduced Risk of Estrogen-Related Cancers by Cigarette Smoking

	Cigarette Smoke Constituent	
	Nicotine	**AhR agonists**
Endometrial Cancer	Aromatase inhibition?	AhR/ER cross talk
Endometrioid Ovarian Cancer	Anti-inflammatory effects? Aromatase inhibition	ER/AhR cross talk
Clear Cell Ovarian Cancer	Anti-inflammatory effects?	ER/AhR cross talk?
Thyroid Cancer	Anti-inflammatory effects? Reduction of TSH levels?	ER/AhR cross talk?

? Entry an unlikely or uncertain contributor to an inverse association with cigarette smoking