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Cigarette Smoking and the Risk of Epithelial Ovarian Cancer: A Review

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By

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MPH, Columbia University, 2007
BS, Stony Brook University, 2005

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An abstract of
a thesis submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of Master of Science in Epidemiology
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Abstract

Cigarette Smoking and the Risk of Epithelial Ovarian Cancer: A Review

By Lauren Elizabeth Murray, MPH

Introduction. Early studies have suggested that there is no association between cigarette smoking and ovarian cancer. However, more recent studies have emerged reporting contradictory evidence, suggesting that the association between cigarette smoking and ovarian cancer not only exists, but is positive.

Objective and Methods. We sought to clarify the relationship between smoking and ovarian cancer, particularly by histological subtype, by conducting a systematic literature review.

Results. Overall, these studies indicate that in comparison to those who have never smoked, past and current smokers are at increased risk of mucinous, but not serous or endometrioid ovarian cancers. Additionally, increased smoking increases the risk of mucinous ovarian cancers.

Conclusion. The literature to date suggests that women who smoke are approximately twice as likely to develop mucinous ovarian cancers compared with women who have never smoked. Primary prevention of mucinous ovarian cancer is possible with an adjustment in behavior, as smoking is a modifiable risk factor.

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Introduction

Ever since the famous Doll/Hill smoking study was conducted in the 1950's [1], cigarette smoking and its associated toxins have become some of the most widely studied carcinogens to date. While it has been shown to have deleterious effects for a multitude of diseases, most notably lung cancer, it is still unclear whether cigarette smoking is a risk factor for epithelial ovarian cancer (which accounts for more than 90% of all ovarian cancers) [2,9,10] one of the major causes of cancer death among women in the United States [3,4,5]. Other potential risk factors for ovarian cancer have been studied in depth, but from an epidemiological perspective, it is imperative to understand the mechanisms by which smoking may increase the risk of ovarian cancer, as smoking rates among girls and women are not only increasing in both the developed and developing worlds, but more importantly, because of its behavioral nature, smoking is an easily modifiable potential cause, unlike some other potential causes.

Evidence which suggests that smoking may lead to impaired ovarian function, including early menopause and subfertility, has been mounting over the past decade or so [5,6,7,8]. A few studies have even suggested that subfertile women may be at increased risk of ovarian and other reproductive cancers [9,11]. Thus, it seems fitting to explore whether smoking does indeed increase the risk of ovarian

cancer, perhaps through the biological mechanism of subfertility and/or subfecundity, or through some other biological mechanism which remains to be expounded.

Of the studies which have attempted to explore the relationship between cigarette smoking and ovarian cancer, very few have addressed the complex and delicate embryology and anatomy of the ovary, which seem to play a role in the biological mechanism by which smoking may cause ovarian cancer. It is known that different histologic cell types in the body have different risk profiles [7,8]; consequently, those tissues and cells are studied accordingly. Therefore, the same logic ought to be applied when doing studies of the ovaries, considering the intricacies of ovarian cells.

Risch, Soegaard, and Purdie have all attempted to tease out the risk-factor profiles for the different types of cells in the ovaries despite the fact that many studies ignore this underlying histological importance [2,8,12,13]. In particular, “Mucinous tumors resemble either the endocervical epithelium or, more frequently, the intestinal epithelium, whereas serous tumors resemble the interior of the fallopian tube. Endometrioid tumors resemble the internal lining of the uterus, clear cell tumors are formed by clear, peglike cells and Brenner tumors resemble the internal lining of the urinary bladder” [2]. Among the studies which have attempted to unearth the relationship between

smoking and epithelial ovarian cancer, taking into account histologic differences, the dominant trend seems to show that smoking is a risk factor for mucinous but not nonmucinous ovarian cancers [2,14-27].

While quantitative methods have not been utilized to make formal assessments , this systematic literature review will attempt to examine and elucidate the relationship between smoking and ovarian cancer, particularly by histologic subtype, as well as offer suggestions for future research.

Methods

In order to identify etiologic studies of smoking and ovarian cancer, a systematic, comprehensive search was performed using the search terms “cigarette smoking or smoking” and “ovarian cancer or ovarian carcinoma” and “mucinous or nonmucinous ovarian” in Medline. Additional studies were identified by searching the reference lists of studies found from the initial Medline search. The objective was to garner substantiated etiologic evidence as opposed to obtaining quantitative estimates of measures of association. Consequently, this review does not utilize formal, quantitative methodology. Rather, we have attempted to be thorough in exploring the evidence to date, and have included all relevant papers identified. Basic calculations, however, including obtaining the proportion of histological cell types among cases, as well as the proportion of smokers among controls, have been performed.

Studies which utilized data from the United States and elsewhere (including Australia, Canada, Norway and Denmark) have been included. Only those which contained a measure of association (OR, RR or HR) have been incorporated. Studies published prior to 2000 were employed for the purpose of obtaining background information, but not for analytical purposes. Pertinent information (such as country in which the study was conducted, year of publication, type of study,

histological subtypes, invasiveness, number of cases/controls or cohort size, smoking status and pack years) has nevertheless been extracted from specific studies. Lastly, although statistical interaction with alcohol intake, physical activity, family history, age at menarche, BMI, HRT use and OC use has been considered, it was not formally assessed using quantitative methods. Rather, studies which investigated some or all of the aforementioned interactions in their statistical analyses were observed qualitatively and their findings have been reported.

Results

Overall, we identified twenty-four studies which examined the relationship between smoking and epithelial ovarian cancers [2,6-28], fifteen of which considered the association with regards to histological subtype [2,14-27]. Of the 15 studies which considered histological subtype, 5 were cohort studies [16,23,25,27,28] and 10 were case-control studies [2,14,15,17,18,20,21,22,24,26], 1 of which was a pooled analyses that merged 10 US-based case-control studies [19]. Additionally, 8 of the 15 aforementioned studies were conducted using US-based data, while 3 were conducted using Australian data, 2 used Canadian data, 1 used Norwegian data, and 1 used Danish data. All 15 studies were carried out and published within the last decade. Most presented results for both borderline and invasive cancers, with merely 3 studies presenting results for invasive cancers only [19,25,28]. Mucinous cancers were the least common in all studies, followed by endometrioid and serous, which dominated the proportion of histologic subtypes among cases in each study population. Moreover, the control populations were mainly non-smokers, with the proportion of current smokers ranging from 13-33% (Table 1).

Table 1: Characteristics of etiologic studies of smoking and ovarian cancer – an example from 17 published studies

Study	Country	Year	Design	Cases/ Controls	Invasiveness	Proportion of Histologic Subtype[a]	Proportion of Smokers among Controls (person-years)	
							Never	Current
Baker	USA	2006	Case-control	434/868	Borderline and Invasive	M 8% S 62% E 12% O 18%	54%	18%
Goodman	USA	2003	Case-control	558/607	Borderline and Invasive	M 20% NM 80%	60%	13%
Pan	Canada	2004	Case-control	442/2,135	Invasive	M 16% NM 84%	51%	20%
Tworoger	USA	2008	Cohort	737/80,253	Borderline and invasive	M 9% NM 91%	53%	19%
Zhang	USA	2003	Case-control	706/1435	Borderline and Invasive	M 10% S 57% E 15% O 18%	50%	28%
Gram	Norway	2007	Cohort	337/101,159	Borderline and Invasive	M 16% S 56% O 28%	59%	24%
Rossing	USA	2008	Case-control	812/1,313	Borderline and Invasive	M 14% S 56% E 12% O 18%	63%	22%
Nagle	Australia	2006	Cohort	676/86,926	Invasive	M 6% S 55% E 15% O 24%	61%	17%
Terry	Canada	2003	Cohort	454/89,835	Invasive	M 7% S 40% E 15% O 38%	51%	22%
Modu	USA	2002	Case-control	767/1,367	Borderline and Invasive	M 15% NM 85%	46%	23%

ngo								
Soegaard	Denmark	2007	Case-control	554/1,564	Borderline and Invasive	M 9% S 62% E 14% O 15%	42%	33%
Kurian	USA	2005	Pooled case-control	2066/7,484	Invasive	M 12% S 52% E 18% O 18%	46%	32%
Jordan 1	Australia	2007	Case-control	363/754	Borderline and Invasive	M 36% S 63%	49%	25%
Jordan 2	Australia	2007	Case-control	323/1,487	Borderline and Invasive	M 100%	46%	30%
Gates	USA	2009	Cohort	876/108,073	Borderline and Invasive	M 10% S 53% E 15% O 22%	Info Not Given	12%
Boyce	USA	2009	Case-control	72/1,578	Invasive	Unidentified	50%	Info Not Given
Green	Australia	2001	Case-control	764/855	Borderline and Invasive	M 14% NM 86%	62%	16%

[a] M: mucinous, NM: non-mucinous, S: serous, E: endometrioid, O: other

- *Mucinous Cancers*

The results of the studies which presented measures of associations (relative risks or odds ratios, depending on study design) for mucinous cancers and current or past smokers compared with those who never smoked are presented in Table 2. Among those that utilized a cohort design [16,23,25,27], all found positive associations, although only 1 study presented statistically significant results [16]. This study indicated a 2-fold increase in the risk of mucinous cancers among both past and current smokers. 1 study [25] reported a borderline, statistically significant, nearly 2.5-fold increase among current smokers.

Among the studies that utilized a case-control design [2,14,15,17-22,24,26], most found positive associations. A few, however, reported protective associations among past smokers [2,21,26], while only one study reported protective associations among current smokers [24], although none of these results were statistically significant. Four studies found statistically significant results for both past and current smokers [14,16-18], while four found statistically significant results for current smokers only compared with never smokers [19-22], and one found statistically significant results for past smokers only compared with never smokers [15]. Of all studies which found positive, statistically significant results, most

found a 2 or 3-fold increase in the risk of mucinous cancers for past or current smokers, compared with never smokers.

Table 2: Measures of association and their corresponding confidence intervals among those with <u>mucinous</u> cancers

	Measure of Association (95% CI)	
Study	**Ever Smoker**	**Current Smoker**
Baker	1.00 (0.34–2.91)	0.79 (0.19–3.25)
Goodman	0.97 (0.60–1.55)	1.22 (0.66–2.26)
Pan	1.77 (1.06–2.96)*	2.36 (1.30–4.29)*
Tworoger	2.02 (1.15–3.55)*	2.22 (1.16–4.24)*
Zhang	2.50 (1.10-5.40)*	1.40 (0.70-2.90)
Gram	1.40 (0.70–2.60)	1.50 (0.70–2.90)
Rossing	1.80 (1.20–2.90)*	2.70(1.60–4.60)*
Terry	1.19 (0.48–2.93)	2.29 (1.00–5.28)*
Modungo	1.90 (1.30-2.90)*	2.70(1.70-4.30)*
Soegaard	0.97 (0.44-2.16)	1.76 (0.92-3.35)
Kurian	1.00 (0.59–1.80)	2.40(1.50–3.80)*
Jordan 1	1.36 (0.84–2.21)	3.25 (1.97–5.34)*
Jordan 2	0.80 (0.40–1.80)	2.10 (1.00–4.60)*
Gates	1.54 (0.94-2.53)	1.52(0.85-2.74)
Green	1.80 (0.80-4.00)	2.30 (1.00-5.40)*

*statistically significant

- *Serous Cancers*

The results of the studies which presented measures of associations serous cancers and current or past smokers compared with those who never smoked are presented in Table 3. Among those that utilized a cohort design [23,25,27], only two studies reported slightly positive associations [23,27], while one reported virtually no association [25]. None of these results was statistically significant.

Among the remaining case-control studies that examined serous cancers in addition to mucinous cancers [2,15,17,19,21,24,26] only two found statistically significant results among current smokers [21,24]. Baker [24] found a statistically significant protective effect, while Jordan [21] found a statistically significant 2-fold positive effect. The remaining studies [2,15,17,19,26] did not find statistically significant results, and most point estimates veered around 1.0, indicating little or no association between past or current smokers and serous ovarian cancers.

Table 3: Measures of association and their corresponding confidence intervals among those with serous cancers

	Measure of Association (95% CI)	
Study	**Ever Smoker**	**Current Smoker**
Baker	0.75 (0.49–1.15)	0.52(0.29–0.95)*
Goodman	0.92 (0.66–1.29)	0.66 (0.37–1.16)
Pan	-	-
Tworoger	-	-
Zhang	0.90 (0.60-1.30)	0.80 (0.50-1.10)
Gram	1.30 (0.90–1.80)	1.30 (0.90–1.90)
Rossing	1.40 (0.90–2.00)	1.10 (0.70–1.90)
Terry	0.98 (0.69–1.40)	1.04 (0.71–1.53)
Modungo	-	-
Soegaard	1.19 (0.89-1.60)	0.85 (0.63-1.13)
Kurian	0.96 (0.75–1.20)	1.00 (0.77–1.3)
Jordan 1	1.22 (0.84–1.76)	2.26(1.45–3.53)*
Jordan 2	-	-
Gates	1.09 (0.89-1.34)	1.14 (0.88-1.49)
Green	-	-

*statistically significant
- results not presented or unavailable

- *Endometrioid Cancers*

The results of the studies which presented measures of associations for endometrioid cancers and current or past smokers compared with those who never smoked are presented in Table 4. Among those that utilized a cohort design [23,25,27], one study presented results indicating no association between past or current smokers and endometrioid cancers [23], while the other two found decreased risk of endometrioid cancers among both past and current smokers [25,27]. Only Gates found a statistically significant result among past smokers [27]. The results from Gram and Terry were not statistically significant [23,25].

Among the remaining case-control studies that examined serous cancers in addition to mucinous cancers [2,15,17,19,24,26], most indicated a slight protective effect or no association at all. None indicated statistically significant results among past or current smokers.

Table 4: Measures of association and their corresponding confidence intervals among those with <u>endometrioid</u> cancers

	Measure of Association (95% CI)	
Study	**Ever Smoker**	**Current Smoker**
Baker	0.93 (0.40–2.14)	0.73 (0.23–2.38)
Goodman	0.74 (0.43–1.29)	0.53 (0.20–1.40)
Pan	-	-
Tworoger	-	-
Zhang	1.00 (0.50-2.10)	0.90 (0.50-1.70)
Gram	1.10 (0.80–1.50)	1.10 (0.80–1.50)
Rossing	0.90 (0.50–1.30)	0.70 (0.30–1.20)
Terry	0.67 (0.37–1.22)	0.81 (0.43–1.54)
Modungo	-	-
Soegaard	1.84 (0.96-3.21)	1.02 (0.56-1.85)
Kurian	0.88 (0.60–1.30)	0.73 (0.48–1.1)
Jordan 1	-	-
Jordan 2	-	-
Gates	0.59(0.39-0.90)*	0.93 (0.59-1.47)
Green	-	-

*statistically significant
- results not presented or unavailable

- *Non-mucinous Cancers*

There were four studies which presented results for only mucinous and non-mucinous cancers without differentiating between more specific histologic subtypes [14,16,18,22]. The results of the studies which presented measures of associations for non-mucinous cancers and current or past smokers compared with those who never smoked are presented in Table 5. Only Tworoger [16] conducted a cohort study, and found no association between non-mucinous cancers and past or current smokers. Among the remaining case-control studies [14,18,22], one indicated a statistically significant positive association among current smokers, with an approximate 1.5-fold increased risk of non-mucinous cancers [22]. The remaining results were neither positive nor statistically significant.

Table 5: Measures of association and their corresponding confidence intervals among those with non-mucinous[a] cancers

	Measure of Association (95% CI)	
Study	**Ever Smoker**	**Current Smoker**
Baker	-	-
Goodman	-	-
Pan	1.13 (0.89–1.44)	0.91 (0.65–1.27)
Tworoger	1.05 (0.86–1.28)	1.06 (0.74–1.51)
Zhang	-	-
Gram	-	-
Rossing	-	-
Terry	-	-
Modungo	1.10 (0.90-1.30)	1.00 (0.80-1.30)
Soegaard	-	-
Kurian	-	-
Jordan 1	-	-
Jordan 2	-	-
Gates	-	-
Green	1.30 (0.90-1.70)	1.60(1.10-2.30)*

[a] If cancer type was not identified explicitly in the study as serous, endometrioid, or other, it was classified as non-mucinous

*statistically significant

- results not presented or unavailable

Discussion

The most significant findings of this review are those pertaining to mucinous cancers and current smoking, although past smoking seems to be positively associated with mucinous cancers as well (Table 2). Of the studies which found not only positive associations, but also statistically significant ones, most found two and three-fold increases in the risk of mucinous cancers.

Looking at these results holistically and according to histological subtype, one can conclude that smokers, particularly current smokers, are at least twice as likely to develop mucinous ovarian cancer when compared with those who have never smoked. This increased risk does not appear to happen immediately upon commencement of smoking, but rather after a prolonged period of time. Furthermore, interactions with alcohol intake, physical activity, family history, age at menarche, BMI, HRT and OC use were found to be statistically insignificant in Terry et al. Of note, effect modification with alcohol intake was found to be statistically insignificant in a pooled cohort study [31], although said study as well as another [32] showed that alcohol consumption increases the risk of mucinous, but not non-mucinous ovarian cancers. Thus, while interaction may have been reported as statistically insignificant in these particular instances, the fact that alcohol consumption was found to increase the risk of mucinous, but not non-

mucinous ovarian cancers further suggests and supports the claim that mucinous tumors differ histologically and etiologically from non-mucinous, as well as other types of tumors.

Many of these studies also examined this relationship by pack-years and cigarettes smoked per day. In many instances, a pack-year was defined as 20 cigarettes or more per day for at least one year [2,14-22,25,27,27], thereby suggesting that this otherwise two-fold risk also increases with increased smoking amounts. However, many of these studies also suggested that the risk returns to baseline once an individual has ceased smoking for a prolonged period of time (at least 20 years) [2,14,17,19,22,23,25]. Only one study [22] found a significant positive association between current smoking and non-mucinous cancers. Terry et al., [25] however, reported a statistically significant increase in the risk of “other” non-mucinous ovarian cancer among former smokers (RR=1.51, 95% CI = 1.06-2.15). None of the studies indicated a significant reduction or increase in serous ovarian cancer among smokers. Although evidence is sparse in the literature, it appears that smokers may be at no or even reduced risk of endometrioid ovarian cancer. Thus, in general, smoking does not appear to increase the risk of non-mucinous epithelial ovarian cancers, although taking into account evidence presented in the Green and

Terry papers, a slight increased risk of serous and other non-mucinous cancers among long-term smokers cannot be entirely disregarded.

Although this systematic literature review did not utilize quantitative methodologies, such as meta-analysis, it offers the potential to look at several studies qualitatively as an amalgamation of the relationship between a factor (smoking) and an outcome (epithelial ovarian cancer) across different study designs. While this is one benefit to conducting such a review, inherent potential sources of error within the included studies cannot be eliminated or overlooked, particularly since the majority of studies examined are case-control by design. As a result, both selection and recall biases must be considered as potential sources of error.

One possible scenario is that controls who chose to partake in the studies had lower prevalences of smoking than the general populations from which they arose. Moreover, controls could have underestimated their level of cigarette use. Both instances could lead to falsely inflated odds ratios, as cases would inherently have been more likely to smoke. Nonetheless, this bias would affect the results for all tumor types equally and therefore does not explain the markedly different patterns seen for mucinous and non-mucinous cancers, or the possible reduced risk seen for endometrioid cancers. Additionally, because confounding could not be assessed directly in

this review, it is impossible to say definitively whether confounding could explain some of the results. However, all of the included studies adjusted for major potential confounders or noted that adjustment did not change the effect estimates significantly. Thus, it is unlikely that confounding occurred.

Of note, all included studies were published within the last decade. Earlier studies on smoking and ovarian cancer tended to find little or no association. It was not until fairly recently that studies with positive associations began to emerge. Thus, publication bias cannot be unequivocally disregarded. It is possible that these more recent studies which show positive associations are simply more likely to be published, as opposed to the older studies which showed little or no association. However, the included pooled case-control analysis accounted for these older studies, as well as some unpublished studies which found no association [19]. Another pooled study [29] also accounted for these older studies, and in both instances, the results were not significantly different. Both studies concluded that smokers were at increased risk of mucinous, but not non-mucinous ovarian cancers. It is unlikely that the unpublished data would have found strong enough protective associations to negate the strong positive associations observed in the published data. The results from the included studies, therefore, are likely not explained by publication bias.

Of the studies which reported no statistically significant association between smoking and mucinous ovarian cancers [2,23,24,26,27] it is worth mentioning that all obtained wide confidence intervals compatible with a two-fold increased risk seen in the studies which showed a positive association. Two of these studies [23,27] had the lowest proportions of current smokers. Consequently, it is possible that they simply did not have enough smokers in the studies to observe an association which would reflect that of the general population. Further, Terry et al. [25] suggested that the observed associations between smoking and ovarian cancer, both mucinous and non-mucinous, may be due, in part, to the fact that the causal action of smoking occurs at different stages in tumor development.

Histologically, mucinous ovarian tumors resemble those of the cervix and gastrointestinal tract. Additionally, cigarette smoking has been shown to be positively associated with cancers of the intestinal epithelium, particularly the pancreas and colon. By contrast, smoking has been shown to reduce the risk of endometrial cancer, which presents histologically similar to endometroid and clear cell ovarian cancers [29,36]. Moreover, aside from containing a multitude of known carcinogens, cigarette smoking is associated with elevated levels of androgens, lower levels of endogenous estrogens, delayed

conception and early menopause [37]. As a result, it is not only biologically plausible that the association between smoking and ovarian cancer exists, but also that said association may differ by histological subtype.

One of the main issues with any epidemiological study is misclassification. Mucinous ovarian cancer is, by nature, difficult to diagnose. As a result of this complication, sometimes mucinous ovarian cancers are misdiagnosed and confused with other mucinous cancers of the surrounding organs and tissues, including the appendix, pancreas, cervix, colon and stomach [35].This issue of misdiagnosis has been recognized only recently, which could also explain the difference in results of older studies versus those conducted in the last decade. It is likely that a proportion of tumors diagnosed as mucinous ovarian cancers were actually gastrointestinal or cervical cancers. However, this still does not explain the observed association between smoking and mucinous ovarian cancers. Because clinicians have improved diagnostic techniques in the last decade, as to avoid misdiagnosis, the studies included in this review have likely utilized enhanced, superior methods, thereby limiting or eliminating the possibility of disease misclassification. In one study, in fact, a group of pathologists reviewed all cases to classify histological subtypes [22].

Since mucinous tumors develop slowly from their benign counterparts (unlike serous tumors which appear to present in malignant form immediately), it is possible that smoking intensifies the progression from benign to malignant [25]. Consequently, many benign ovarian tumors may have otherwise remained as such were it not for the presence of smoking, which may act as a biological catalyst. Another argument presented in Terry et al. suggests that women who actively smoke may inherently suffer other ailments, thereby encouraging them to seek medical attention more often than women who do not smoke. Considering that both mucinous and non-mucinous ovarian tumors are typically large, they may be diagnosed during routine physical examinations, suggesting that associations observed between smoking and ovarian cancer may be a result of detection bias [25].

Future research should include both quantitative and qualitative approaches (including, but not limited to examining the biological mechanism by which subfertile women may be at increased risk of ovarian and other reproductive cancers), as well as focus on differentiating the relationship of interest based on cell type. Particularly, in studies which use medical chart review methods, it is imperative to employ not only the insight of medical expects, but also to utilize sound molecular techniques, such as genomic and proteomic

profiling [19] to more accurately classify tumor subtypes. Studies which do not differentiate between histological subtypes will likely produce misleading results. Moreover, future investigators ought to be wary of combining ex-smokers with current or never smokers. As we've observed, both current and former smokers were found to be at increased risk of mucinous ovarian tumors. Thus, it is methodologically inappropriate to coalesce smoking categories, as this would result in exposure misclassification and ultimately bias results away from the null. Lastly, it would be particularly advantageous to conduct studies in populations which have already been screen for ovarian cancer, as to avoid detection bias altogether. Only with such information can the relationship between smoking and ovarian cancer be truly expounded.

In conclusion, this systematic review suggests that women who smoke consistently are approximately twice as likely to develop mucinous ovarian cancers compared with women who have never smoked. Although this risk seems to increase with increase smoking amounts, evidence suggests that the risk returns to baseline once smoking has been ceased for a prolonged period of time. Thus, primary prevention of mucinous ovarian cancers is very possible with behavior modification.

References

1. Doll R, et al. *Mortality in relation to smoking: 22 years' observations on female British doctors.* Br J Med. 1980. April 5:967–9.

2. Soegaard M, Jensen A, Høgdall E, Christensen L, Høgdall C, Blaakaer J, Kjaer SK. *Different risk factor profiles for mucinous and nonmucinous ovarian cancer: results from the Danish MALOVA study.* Cancer Epidemiol Biomarkers Prev. 2007 Jun;16(6):1160-6.

3. American Cancer Society. Cancer facts and figures 2002. New York, NY: American Cancer Society, 2002.

4. Ferlay J, et al. *GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide*. IARC Cancer Base, vol. 5. Lyon: IARCPress;
2004. version 2.0.

5. Bertone-Johnson ER. *Epidemiology of ovarian cancer: a status report.* Lancet 2005; 365(9454):101–2.

6. Purdie DM, Siskind V, Bain CJ, Webb PM, Green AC. *Reproduction-related risk factors for mucinous and nonmucinous epithelial ovarian cancer.* Am J Epidemiol. 2001 May 1;153(9):860-4.

7. Risch HA. *Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone.* J Natl Cancer Inst. 1998 Dec 2;90(23):1774-86. Review.

8. Risch HA, Marrett LD, Jain M, Howe GR. *Differences in risk factors for epithelial ovarian cancer by histologic type. Results of a case-control study.* Am J Epidemiol. 1996Aug15;144(4):363-72.

9. Tung KH, Goodman MT, Wu AH, McDuffie K, Wilkens LR, Kolonel LN, Nomura AM, Terada KY, Carney ME, Sobin LH. *Reproductive factors and epithelial ovarian cancer risk by histologic type: a multiethnic case-control study.* Am J Epidemiol. 2003 Oct 1;158(7):629-38.

10. Modugno F, Ness RB, Wheeler JE. *Reproductive risk factors for epithelial ovarian cancer according to histologic type and invasiveness.* Ann Epidemiol. 2001 Nov;11(8):568-74.

11. Booth M, Beral V, Smith P. *Risk factors for ovarian cancer: a case-control study.* Br J Cancer. 1989 Oct;60(4):592-8.

12. Risch HA, Weiss NS, Lyon JL, Daling JR, Liff JM. *Events of reproductive life and the incidence of epithelial ovarian cancer.* Am J Epidemiol. 1983 Feb;117(2):128-39.

13. Purdie DM, Webb PM, Siskind V, Bain CJ, Green AC. *The different etiologies of mucinous and nonmucinous epithelial ovarian cancers.* Gynecol Oncol. 2003 Jan;88(1 Pt 2):S145-8.

14. Pan SY, Ugnat AM, Mao Y, Wen SW, Johnson KC; Canadian Cancer Registries Epidemiology Research Group. *Association of cigarette smoking with the risk of ovarian cancer.* Int J Cancer. 2004 Aug 10;111(1):124-30.

15. Zhang Y, Coogan PF, Palmer JR, Strom BL, Rosenberg L. *Cigarette smoking and increased risk of mucinous epithelial ovarian cancer.* Am J Epidemiol. 2004 Jan 15;159(2):133-9.

16. Tworoger SS, Gertig DM, Gates MA, Hecht JL, Hankinson SE. *Caffeine, alcohol, smoking, and the risk of incident epithelial ovarian cancer.* Cancer. 2008 Mar 1;112(5):1169-77.

17. Rossing MA, Cushing-Haugen KL, Wicklund KG, Weiss NS. *Cigarette smoking and risk of epithelial ovarian cancer.* Cancer Causes Control. 2008 May;19(4):413-20. Epub 2007 Dec 15.

18. Modugno F, Ness RB, Cottreau CM. *Cigarette smoking and the risk of mucinous and nonmucinous epithelial ovarian cancer.* Epidemiology. 2002 Jul;13(4):467-71.

19. Kurian AW, Balise RR, McGuire V, Whittemore AS. *Histologic types of epithelial ovarian cancer: have they different risk factors?* Gynecol Oncol. 2005 Feb;96(2):520-30.

20. Jordan SJ, Green AC, Whiteman DC, Webb PM; Australian Ovarian Cancer Study Group. *Risk factors for benign, borderline and invasive mucinous ovarian tumors: epidemiological evidence of a neoplastic continuum?* Gynecol Oncol. 2007 Nov;107(2):223-30. Epub 2007 Jul 27.

21. Jordan SJ, Green AC, Whiteman DC, Webb PM. *Risk factors for benign serous and mucinous epithelial ovarian tumors.* Obstet Gynecol. 2007 Mar;109(3):647-54.

22. Green A, Purdie D, Bain C, Siskind V, Webb PM. *Cigarette smoking and risk of epithelial ovarian cancer (Australia).* Cancer Causes Control. 2001 Oct;12(8):713-9.

23. Gram IT, Braaten T, Adami HO, Lund E, Weiderpass E. *Cigarette smoking and risk of borderline and invasive epithelial ovarian cancer.* Int J Cancer. 2008 Feb 1;122(3):647-52.

24. Baker JA, Odunuga OO, Rodabaugh KJ, Reid ME, Menezes RJ, Moysich KB. *Active and passive smoking and risk of ovarian cancer.* Int J Gynecol Cancer. 2006 Jan-Feb;16 Suppl 1:211-8.

25. Terry PD, Miller AB, Jones JG, Rohan TE. *Cigarette smoking and the risk of invasive epithelial ovarian cancer in a prospective cohort study.* Eur J Cancer. 2003 May;39(8):1157-64.

26. Goodman MT, Tung KH. *Active and passive tobacco smoking and the risk of borderline and invasive ovarian cancer (United States).* Cancer Causes Control. 2003 Aug;14(6):569-77.

27. Gates MA, Rosner BA, Hecht JL, Tworoger SS. *Risk factors for epithelial ovarian cancer by histologic subtype.*Am J Epidemiol. 2010 Jan 1;171(1):45-53. Epub 2009 Nov 12.

28. Nagle CM, Bain CJ, Webb PM. *Cigarette smoking and survival after ovarian cancer diagnosis.* Cancer Epidemiol Biomarkers Prev. 2006 Dec;15(12):2557-60.

29. Jordan SJ, Whiteman DC, Purdie DM, Green AC, Webb PM. *Does smoking increase risk of ovarian cancer? A systematic review.* Gynecol Oncol. 2006 Dec;103(3):1122-9. Epub 2006 Sep 26.

30. Boyce EA, Costaggini I, Vitonis A, Feltmate C, Muto M, Berkowitz R, Cramer D, Horowitz NS. *The epidemiology of ovarian granulosa cell tumors: a case-control study.* Gynecol Oncol. 2009 Nov;115(2):221-5. Epub 2009 Aug 7.

31. Genkinger JM, Hunter DJ, Spiegelman D, et al. *Alcohol intake and ovarian cancer risk: a pooled analysis of 10 cohort studies.* Br J Cancer. 2006 Mar 13;94(5):757-62.

32. Modugno F, Ness RB, Allen GO. *Alcohol consumption and the risk of mucinous and nonmucinous epithelial ovarian cancer.* Obstet Gynecol. 2003 Dec;102(6):1336-43.

33. Niwa Y, Wakai K, Suzuki S, Tamakoshi K, et al. *Cigarette smoking and the risk of ovarian cancer in the Japanese population: findings from the Japanese Collaborate Cohort study.* J Obstet Gynaecol Res. 2005 Apr;31(2):144-51.

34. Ness RB, Cramer DW, Goodman MT, et al. *Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case– control studies.* Am J Epidemiol. 2002 155: 217–224.

35. Tavassoli FA, Devilee P. World Health Organization classification of tumors. *Pathology and genetics of tumors of the breast and female genital organs.* Lyon: IARC Press; 2003.

36. Berrington de Gonzalez A, Sweetland S, Green J. *Comparison of risk factors for squamous cell and adenocarcinomas of the cervix: a metaanalysis*. Br J Cancer 2004;90(9):1787–91.

37. Tanko LB, Christiansen C. *An update on the antiestrogenic effect ofsmoking: a literature review with implications for researchers and practitioners*. Menopause 2004;11(1):104–9.