Short Communication

Height, Age at Menarche, and Risk of Epithelial Ovarian Cancer

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Abstract

Objective: **We hypothesized that the hormonal changes of adolescence influence ovarian cancer risk particularly in younger women. We investigated this possibility by examining the relationship between ovarian cancer and adult height and age at menarche as both factors reflect pubertal hormonal levels.**
Methods: **Participants were a population-based sample of women with incident ovarian cancer ($n = 794$) and control women randomly selected from the Australian Electoral Roll ($n = 855$). The women provided comprehensive reproductive and lifestyle data during a standard interview.**
Results: **Although neither height nor age at menarche was significantly related to the risk of ovarian cancer overall, increasing height was associated with increasing risk of the subgroup of mucinous borderline ovarian cancer (odds ratio, 5.3; 95% confidence interval, 1.5-19.1 for women $\geq$175 cm compared with women <160 cm, P_{trend} = 0.02). Similarly, later age at menarche was associated with increasing risk of mucinous borderline cancers (odds ratio, 3.8; 95% confidence interval, 1.3-11.4 for those with age at menarche $\geq$14 years compared with those <12 years, P_{trend} = 0.003). Women with mucinous borderline cancers were significantly younger than the women diagnosed with invasive cancers (mean 44 versus 57 years; P < 0.0001).**
Conclusions: **Development of mucinous borderline ovarian cancers, predominantly diagnosed in women ages under 50 years, seems to be associated with age at menarche and attained adult height. These results are consistent with our original hypothesis that pubertal levels of reproductive hormones and insulin-like growth factor-I influence ovarian cancer risk in younger women.** (Cancer Epidemiol Biomarkers Prev 2005;14(8):2045–8)

Introduction

Changes in sex hormones in a woman during her 20s and 30s are important in the pathogenesis of epithelial ovarian cancer as seen by the clear effects of pregnancy and the oral contraceptive pill on the risk of developing the disease, most of which is diagnosed in women over the age of 50. Therefore, we hypothesized that the major sex and growth hormonal changes that occur in late childhood and early adolescence influence the risk of epithelial ovarian cancer (hereafter ''ovarian cancer''), particularly in younger women. We investigated this possibility by examining in detail the relationship between the occurrence of ovarian cancer and women's attained adult height and age at menarche because both factors are strongly influenced by the peripubertal hormonal milieux.

Relatively few studies have examined the relationship between height and ovarian cancer risk. Whereas these studies suggest an increased ovarian cancer risk overall with odds ratios (OR) between 1.2 and 2.8 for the tallest women (variously $\geq$168-177 cm) versus the shortest women (152-167 cm; refs. 1-4), larger effects have been reported for serous borderline (OR, 3.10 for women $\geq$168 cm versus those <168 cm; ref. 5) and invasive endometrioid (2) subtypes and among women diagnosed at a younger age (2, 5, 6). On the

other hand, the effect of age at menarche on ovarian cancer risk has been investigated frequently and no significant association has been reported either overall (7-9) or according to histologic subtype (10-12). Whether the association with age at menarche as a reflection of peripubertal sex hormone levels might vary according to age at diagnosis of ovarian cancer does not seem to have been investigated. Our *a priori* hypothesis was that hormone levels in late childhood and adolescence would be most important in the development of cancers in women of a younger age, whereas in older women the effect of peripubertal hormones would be attenuated. We were especially interested in the possible influences of insulin-like growth factor-I (IGF-I) and thus specifically predicted positive associations with height analogous to observations for breast cancer. As previous studies have suggested that mucinous ovarian cancers are etiologically different from the other histologic subtypes of ovarian cancer (13-15), we also considered that relationships with peripubertal factors might vary according to subtype.

Materials and Methods

We assessed the relationships between height and age at menarche and ovarian cancer risk using data from an Australian population–based case-control study undertaken between 1990 and 1993. The methods have been described elsewhere (8). Briefly, women aged 18 to 79 years with newly diagnosed primary epithelial ovarian cancer were ascertained through gynecology-oncology treatment centers in eastern states of Australia. An expert gynecologic histopathologist in each state reviewed pathology reports and sections of each of the tumors to confirm the diagnosis of epithelial ovarian cancer and the histologic subtype of the tumors. Any

discrepancies with the original reporting were resolved by discussion and consensus between pathologists. Ninety percent ($n = 794$) of eligible women participated. Control women were randomly selected from the Australian Electoral Roll after stratifying by age and geographic region. Enrollment to vote is compulsory throughout Australia with coverage estimated to be ~95% (16). Women were ineligible to take part if they had a history of ovarian cancer or bilateral oophorectomy. In total, 73% ($n = 855$) of eligible control women agreed to participate. All of the women provided informed consent and were interviewed face to face by trained interviewers. They provided demographic, lifestyle, and reproductive information. Height was divided at 5 cm intervals to create five groups for comparison, with women <160 cm tall as the reference group. Age at menarche was divided into four groups with age at menarche of <12 years as the reference group. ORs and 95% confidence intervals (95% CI) were calculated as estimates of the relative risk of ovarian cancer using multiple logistic regression to simultaneously adjust for potential confounding factors. Analyses by histologic subtype of ovarian cancer were undertaken using polytomous regression. The cases were first divided according to invasiveness such that the response categories were controls, invasive cancers, and borderline cancers. The case group was further divided into serous invasive, endometrioid invasive, mucinous invasive, serous borderline, and mucinous borderline cancers to simultaneously compare each group with controls. Other subtypes included too few cases for analysis. Factors known to influence ovarian cancer risk in our study population were included in the models and those that materially changed estimates or were potentially associated with both ovarian cancer risk and height and/or age at menarche were included in the final models. Women with missing data were excluded from each of the current analyses.

Results

A summary of demographic and risk factor data for study participants is provided in Table 1. As in other studies of ovarian cancer, women with ovarian cancer were less likely to have taken the oral contraceptive pill or to have had a hysterectomy or tubal sterilization than control women, and were more likely to have a family history of ovarian cancer and to have had fewer children.

Overall, height was not significantly related to risk of ovarian cancer (Table 2) and this did not change when the data were stratified according to age (≤55 versus >55 years, the mean age in case women) or the menopausal status of the women (results not shown). However, when histologic subtypes were analyzed, the tallest women (≥175 cm tall) had a 5-fold increased risk of mucinous borderline ovarian cancers compared with the shortest women (<160 cm) and the trend of increasing risk with increasing height was significant (OR, 5.27; 95% CI, 1.45-19.08, P_{trend} 0.02). We had expected that height would influence risk particularly for younger women and, indeed, women diagnosed with mucinous borderline ovarian cancers had a mean age of 44 years, which was significantly younger than women who presented with invasive ovarian cancers (mean age, 57; $P < 0.0001$). There were too few women with borderline mucinous cancers to look for a modifying effect of age at diagnosis within this subgroup.

The results were similar in relation to age at menarche with no overall association with risk of ovarian cancer (Table 3). However, women who experienced menarche at 14 years old or later had almost four times the risk of mucinous borderline ovarian cancers compared with those experiencing menarche at <12 years of age (OR, 3.82; 95% CI, 1.28-11.43; $P_{trend} = 0.003$).

Because it is possible that both attained adult height and age at menarche reflect similar factors (genetic, nutritional, and hormonal), they were included in the model simultaneously, but the terms for each remained significant and the ORs for each did not materially change. We also checked for effect modification of height by menarche (divided at the median) and vice versa and although no modification was seen, our subgroups became too small to reliably test for interactions.

Women with serous borderline cancers were also diagnosed at a relatively young age (mean age at diagnosis, 45 years) but, in contrast to those with mucinous borderline cancers,

Table 1. Demographic and risk factor data for study participants

Factor	Group (n)						
	Controls (829)	All cases (764)	Serous invasive (342)	Endometrioid invasive (148)	Mucinous invasive (48)	Serous borderline (61)	Mucinous borderline (62)
Age (y, mean)	54	55	58	57	50	46	45
Parity							
0	15% (131)	22% (164)	16% (55)	29% (43)	21% (10)	28% (17)	26% (16)
1-2	15% (123)	43% (329)	44% (150)	43% (63)	44% (21)	46% (28)	40% (25)
≥3	46% (382)	36% (271)	40% (137)	28% (42)	35% (17)	26% (16)	34% (21)
Family history of breast or ovarian cancer (yes)	8% (64)	12% (88)	16% (54)	9% (13)	6% (3)	12% (7)	2% (1)
Ever use oral contraceptives	64% (534)	50% (381)	47% (161)	43% (64)	60% (29)	64% (39)	69% (43)
Hysterectomy (yes)	20% (168)	14% (109)	16% (54)	10% (14)	19% (9)	12% (7)	10% (6)
Tubal ligation (yes)	23% (188)	13% (102)	14% (47)	12% (17)	17% (8)	10% (6)	10% (6)
Post school education (yes)	48% (400)	42% (318)	40% (138)	45% (67)	44% (21)	34% (21)	50% (31)
Smoking status							
Never	63% (521)	58% (446)	62% (212)	65% (96)	48% (23)	56% (34)	36% (22)
Current	15% (126)	20% (150)	14% (46)	19% (28)	27% (13)	16% (17)	37% (23)
Past	22% (182)	22% (168)	25% (84)	16% (24)	25% (12)	28% (10)	27% (17)
Height (cm)							
<160	34% (283)	33% (248)	34% (116)	36% (53)	35% (17)	36% (22)	11% (7)
160-164	28% (232)	31% (240)	33% (112)	28% (41)	33% (16)	31% (19)	36% (22)
165-169	23% (194)	20% (156)	18% (63)	26% (38)	13% (6)	18% (11)	19% (12)
170-174	11% (94)	12% (89)	10% (35)	9% (13)	15% (7)	13% (8)	24% (15)
≥175	3% (26)	4% (31)	5% (16)	2% (3)	4% (2)	2% (1)	10% (6)
Menarche age (y)							
<12	16% (132)	15% (116)	13% (46)	18% (27)	13% (6)	21% (13)	7% (4)
12	19% (158)	18% (137)	20% (69)	18% (27)	19% (9)	15% (9)	10% (6)
13	27% (221)	27% (208)	26% (90)	24% (35)	21% (10)	38% (23)	39% (24)
≥14	38% (318)	40% (303)	40% (137)	40% (59)	48% (23)	26% (16)	45% (28)

Table 2. ORs for the relationship between height and the risk of epithelial ovarian cancer by ovarian cancer type

Height (cm)	Adjusted OR* (95% CI)							
	All cancers ($n = 764$)	All invasive ($n = 630$)	All borderline ($n = 134$)	Invasive serous ($n = 342$)	Invasive endometrioid ($n = 148$)	Invasive mucinous ($n = 48$)	Borderline serous ($n = 61$)	Borderline mucinous ($n = 62$)
<160[†]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
160-164	1.17 (0.91-1.52)	1.11 (0.84-1.46)	1.81 (1.08-3.05)	1.16 (0.83-1.60)	0.99 (0.62-1.57)	1.24 (0.60-2.58)	0.98 (0.50-1.92)	**4.52 (1.82-11.18)**
165-169	0.84 (0.63-1.13)	0.87 (0.64-1.18)	0.89 (0.49-1.62)	0.75 (0.51-1.10)	1.12 (0.69-1.84)	0.47 (0.17-1.26)	0.49 (0.22-1.08)	**2.10 (0.77-5.74)**
170-174	1.00 (0.69-1.45)	0.89 (0.60-1.32)	1.53 (0.80-2.91)	0.85 (0.53-1.37)	0.97 (0.48-1.93)	1.08 (0.40-2.90)	0.64 (0.26-1.59)	**4.67 (1.68-12.96)**
≥175	1.24 (0.69-2.22)	1.28 (0.69-2.40)	1.26 (0.47-3.40)	1.41 (0.70-2.84)	0.86 (0.24-3.12)	0.87 (0.17-4.33)	0.26 (0.03-2.14)	**5.27 (1.45-19.08)**
P_{trend}	0.79	0.66	0.74	0.55	0.93	0.53	0.06	**0.021**

*Adjusted for age (in years), age at menarche (<12, 12, 13, ≥14), weight at age 20 (in kg, <50, 50-<55, 55-<60, ≥60), ever use of oral contraceptives (yes/no), and parity (0, 1-2, 3+).
[†]Reference group.

increasing height was associated with a nonsignificant decrease in risk (OR, 0.26; 95% CI, 0.03-2.14 for the tallest women compared with the shortest; P_{trend} = 0.06), as was increasing age at menarche (OR, 0.69; 95% CI, 0.31-1.51).

We also sought to evaluate whether the risks for mucinous borderline tumors in relation to height and age at menarche were significantly different from those for the other tumor types. Using polytomous regression, we set serous invasive cancers as the reference group. Mucinous borderline cancers were the only group that were significantly different from serous invasive cancers with respect to the effects of height and age at menarche (P = 0.01 for each variable modeled as a continuous term).

Discussion

The independent relationships we have found between both height and age at menarche and risk of mucinous borderline ovarian cancer are consistent with our theory that events in childhood and adolescence are important determinants of risk of ovarian cancer in relatively young women but have less impact on risk as women get older. We did not predict *a priori* that the effect would be specific for the mucinous subtype; however, as previous studies have suggested that mucinous cancers are etiologically different (13, 15), the subtype difference was not unexpected. There are several possible explanations for the lack of effect found for invasive mucinous cancers. First, women with invasive mucinous cancer are generally older (mean age, 49 versus 44 years in our study) leading to attenuation of the hypothesized relationships. There were too few women diagnosed with invasive mucinous cancer under the age of 50 years to test formally for an interaction with age. Another possible explanation is histologic misclassification. Recent advances in histopathology have

shown that invasive mucinous ovarian cancers are less common than previously thought (17, 18) and that some of the tumors classified as primary mucinous invasive cancers may have actually been, for example, metastatic intestinal cancers. Mucinous borderline cancers are less likely to be misclassified (18).

Associations such as these have not been reported previously. Indeed, only one published study has examined the relationship between age at menarche and mucinous borderline ovarian cancers and no association was found (11). The average age at diagnosis among women with mucinous borderline cancers in that study was 62 years, much older than the average age seen here and in other studies (14, 19, 20).

Greater height has, however, consistently been found to be a risk factor for breast cancer with IGF-I, a potent mitogen and inhibitor of apoptosis, a suggested mediator of this effect (21). Height may be a marker of total and bioavailable IGF-I levels during the prepubertal growth spurt (22). Elevated serum IGF-I has been associated with increased risk of breast cancer in premenopausal women (23) and the one cohort study that has investigated the association for ovarian cancer reported that the highest IGF-I levels were associated with a significant 5-fold increase in risk of ovarian cancer only in those women diagnosed before the age of 55 (24). It seems that for these two hormonally responsive cancers, IGF-I is influential only in the development of cancer at a younger age.

Peripubertal levels of sex hormones vary with the timing of menarche and may explain the association we have found between age at menarche and risk of mucinous borderline cancers. Compared with girls who have menarche before 12, girls with later menarche have lower levels of estradiol (25), take longer to develop ovulatory cycles after menarche (26, 27), and are therefore relatively progesterone deficient for several years. Progestins may increase apoptosis in ovarian epithelium (28), so women with later menarche may have several extra

Table 3. ORs for the relationship between age at menarche and the risk of epithelial ovarian cancer by ovarian cancer type

Age at menarche (y)	Adjusted ORs* (95% CI)							
	All cancers ($n = 764$)	All invasive ($n = 630$)	All borderline ($n = 134$)	Invasive serous ($n = 342$)	Invasive endometrioid ($n = 148$)	Invasive mucinous ($n = 48$)	Borderline serous ($n = 61$)	Borderline mucinous ($n = 62$)
<12[†]	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
12	1.00 (0.70-1.41)	1.05 (0.73-1.52)	0.84 (0.42-1.71)	1.25 (0.80-1.95)	0.80 (0.44-1.45)	1.31 (0.45-3.80)	0.61 (0.25-1.51)	**1.34 (0.36-4.95)**
13	1.02 (0.74-1.41)	0.94 (0.67-1.33)	1.31 (0.72-2.36)	1.16 (0.76-1.77)	0.66 (0.38-1.16)	0.91 (0.32-2.59)	0.96 (0.46-2.01)	**3.18 (1.06-9.56)**
≥14	1.10 (0.81-1.50)	1.05 (0.76-1.45)	1.34 (0.74-2.43)	1.18 (0.80-1.77)	0.80 (0.48-1.35)	1.85 (0.72-4.74)	0.69 (0.31-1.51)	**3.82 (1.28-11.43)**
P_{trend}	0.44	0.88	0.15	0.62	0.46	0.19	0.61	**0.003**

*Adjusted for age (in years), weight at age 20 (<50, 50-<55, 55-<60, ≥60), parity (0, 1-2, 3+), ever use of oral contraceptives (yes/no), and height (<160, 160-164, 165-169, 170-174, ≥175 cm).
[†]Reference group.

years of low-level estrogen (or other hormone) stimulation of their ovarian epithelium in the absence of the apoptotic effects of progesterone, possibly increasing the chance of the cells acquiring genetic damage. Androgens, which have been shown to stimulate DNA synthesis and decrease cell death in ovarian cell culture lines (29), are also relatively abundant in girls with later menarche (26). The hormonal milieu associated with later menarche may, therefore, be important in the initiation of neoplastic transformation of the ovarian epithelium, perhaps specifically to the mucinous subtype.

The possibility that our results are the result of confounding, bias, or chance must be considered. The strength of the associations we have found makes it unlikely that they are due solely to confounding and because this study was population-based and participation rates were relatively high, the effects of selection bias should be minimal. It is unlikely that women with borderline tumors would systematically overestimate their height and/or age at menarche compared with women with other types of tumor, thus ruling out recall bias as an explanation. Chance is the most likely alternative explanation for our findings. We have examined a number of different subgroups; thus, it is possible that we could have seen a significant result in one subgroup by chance alone. We believe this is unlikely for two reasons. First, borderline mucinous cancers arise most commonly in younger women and our *a priori* hypothesis was that the effects of height and age at menarche would be strongest for cancers diagnosed at an early age. Second, the increased risks we observed in relation to both factors were seen consistently for borderline mucinous cancers alone and both factors were associated with significant trends.

In conclusion, we have found significant trends of increasing risk of mucinous borderline ovarian cancer with increasing adult height and later age at menarche. Women diagnosed with mucinous borderline cancers tend to be younger and our results suggest that prepubertal and peripubertal levels of estrogen, progesterone, androgen, and IGF-I, which are known to influence height and age at menarche, may play important roles in the initiation of mucinous ovarian cancers. Our findings also support the proposition that different etiologic pathways exist for mucinous and nonmucinous ovarian cancers (13).

Acknowledgments

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