Central Adiposity as a Major Risk Factor of Ovarian Cancer

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Abstract. The identification of risk factors for ovarian cancer is crucial in prevention of the disease. This pathology is the leading cause of death from gynecological malignancies. The aim of this study was to evaluate the role of factors influencing hormonal levels such as body mass index (BMI), BMI at age 20, waist-to-hip ratio (WHR), oral contraceptive (OC) use, and risk of ovarian cancer. A case-control study was conducted in women who developed ovarian cancer. Logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (95% CI). While no association was found between BMI, BMI at age 20 and risk of ovarian cancer, high WHR increased the risk with ORs of 2.93 and 8.58 (p<10^-6) for the highest categories (WHR=0.801-0.85 and WHR>0.85) versus the lowest (WHR<0.8). Central adiposity is a key factor in ovarian cancer and suggests the involvement of androgen conversion in adipose tissue.

Ovarian cancer is the leading cause of death among gynecological malignancies and the fifth most frequent cause of cancer among French women with 4,488 new cases and 3,508 deaths reported in 2000 (1). This pathology is often diagnosed at an advanced stage that results in poor prognosis and a high mortality rate. The identification of risk factors may help prevent the disease (2).

Reproductive and hormonal factors modulate the risk of ovarian cancer. Factors influencing ovulation are known to be crucial for ovarian oncogenesis, and chronic repeated ovulation without pregnancy is thought to contribute to neoplasia in the ovarian epithelium (3). Therefore oral contraceptive (OC) use and breastfeeding are considered protective factors, the former eliminating and the latter suppressing ovulation.

Adiposity is associated with hormone-responsive carcinomas, particularly breast cancer. A large prospective study has shown that excess weight and obesity increased the risk of mortality from malignancies such as postmenopausal breast cancer or colon cancer (4), although the data were inconclusive for ovarian cancer. Adiposity alters hormone levels and ovulatory functions, and Risch has described the role of androgens and progesterone in the ovarian epithelium and concluded that the risk of ovarian cancer was increased by excessive androgenic stimulation of ovarian epithelial cells and reduced by greater progesterone stimulation (2). Thus an increase in the bulk of adipose tissue, which induces ovarian and extra-ovarian estrogen synthesis, may play a major role in ovarian cancer.

The aim of this study was to evaluate the role of factors that modulate hormonal levels on the risk of ovarian cancer. Interest was focused on adiposity (body mass index [BMI], BMI at age 20, waist-to-hip ratio [WHR]) and changes in BMI between age 20 and the present age. The role of standard hormonal factors such as age at menarche, length of menstrual cycle, breastfeeding and OC use were also investigated.

Patients and Methods

Population. Fifty-five women aged 24-84 years who had been diagnosed with ovarian cancer with no BRCA mutation were enrolled in the COSA (Breast and Ovarian Cancer in Auvergne) program between November 1996 and November 1999 in different hospitals within the Auvergne region of France. A control population (n=857) was gathered in 2005 and 2006 in a mammographic screening center. The majority of volunteers were women who went for screening in response to the Organized Regional Screening Program Association (ARDOC). This program consisted of inviting all women from the Auvergne region for a free mammography read by two independent radiologists. Eligible controls were women with no previous history of cancer, no more
than one first degree relative breast or ovarian cancer and resident in Auvergne. All the cases and controls were interviewed after giving informed consent.

**Personal interviews.** Interviews were conducted at the Centre Jean Perrin in Clermont-Ferrand. Questionnaires were filled in by the patients at the time of the clinic appointment or later at home. The control population was interviewed at the medical center at the time of enrollment.

The questionnaire included information about reproductive history (including parity, time of nursing, age at menarche, menstrual regularity, age at menopause), use and duration of OCs, anthropometric characteristics (height, weight, weight at age 20, waist and hip measurements) which were measured at the clinical appointment or during the recruitment interview at the medical center for the control population. “Ever use” of OC was defined as at least 3 months of use.

**Data analysis.** The software SEM was used for data analysis (Centre Jean Perrin, Clermont Ferrand, France) (5). Univariate analysis was performed, and odds ratios (ORs) with corresponding 95% confidence intervals (95% CI) were calculated as the primary measures. WHR were categorized in quartiles, in which the two first quartiles were combined. BMI was divided into quartiles with standard cut-offs (<20 kg/m², 20-25 kg/m², 25.1-30 kg/m², >30.1 kg/m²).

Multivariate models were used to select independent parameters or parameters that had specific and significant influence on the risk of ovarian cancer. The model used for multiparametric analysis was a logistic regression (threshold: \( p \leq 0.05 \)), including the calculation of the OR and 95% CI.

## Results

The baseline characteristics of the cases and controls are reported in Table I. The mean age at diagnosis of the cases was 58.4 years and the mean age of the controls was 57.7 years. The menopausal status was equivalent in the two groups. Menopausal women represented 73% of the cases and 74% of the controls.

The age at menarche was not statistically different between the cases and controls (Table I). The OR for age at menarche before or after 12 years old did not show any influence on the risk of ovarian cancer (OR=1.50, 95% CI=0.83-2.68) (Table II). The effect of menstrual cycle length on the risk of ovarian cancer was also investigated and a reduction in risk was found with short or long cycles compared to standard cycles (\( p=0.029 \)). Menopausal status did not seem to be associated with the risk of ovarian cancer (OR=0.72, 95% CI=0.31-1.65).

The duration of lactation was greater among the cases (11.7 weeks) than the controls (7.5 weeks) (\( p=0.15 \)), and the OR showed that the longer the duration of breastfeeding, the greater was the risk of ovarian cancer. The risk was almost doubled for 18 weeks of lactation (OR=1.86, 95% CI=0.92-3.76) (Table II).

### Table I. Baseline characteristics of cases and controls.

|                          | Cases (n=55) |  | Controls (n=857) |  |  |
|--------------------------|-------------|--------------------------|
|                          | Mean age (years) | Range | Mean age (years) | Range | p-Value |
| Age at study             | 58.40       | (33-84) | 57.70       | (24-85) | 0.74 |
| Age at menarche          | 13.04       | (11-16) | 12.95       | (9-19)  | 0.46 |
| Age at natural menopause | 49.30       | (44-60) | 50.30       | (35-61) | 0.35 |
| Breastfeeding (weeks)    | 11.7        | ± 20.3 | 7.5         | ± 15.8 | 0.15 |
| Parity                   | 1.9         | ± 1.2  | 1.8         | ± 1.0  | 0.49 |
| BMI                      | 24.1        | ± 6.0  | 24.0        | ± 4.1  | 0.29 |
| BMI at 20 years old      | 21.1        | ± 2.5  | 20.4        | ± 2.4  | 0.13 |
| Height (cm)              | 160.8       | ± 5.8  | 161.7       | ± 5.8  | 0.31 |
| Waist measurement (cm)   | 86.5        | ± 15.2 | 80.0        | ± 11.4 | <0.001 |
| Hip measurement (cm)     | 99.2        | ± 13.5 | 99.1        | ± 9.1  | 0.91 |
| WHRb                     | 0.87        | ± 0.1  | 0.81        | ± 0.07 | <0.001 |

BMI, Body mass index; WHR, waist-to-hip ratio; SBR, Scarff-Bloom-Richardson.
A decrease in the risk of ovarian cancer was observed among the women who used OCs in comparison to never users (OR=0.18, 95% CI=0.09-0.36) (Table II). This result was not affected by the duration \( (p=0.11) \) or the age at first OC use \( (p=0.55) \).

The study of a possible association between anthropometric characteristics and the risk of ovarian cancer was more complex. BMI and BMI at age 20 were similar between the cases and controls (Table I). No difference in the risk of ovarian cancer was observed with the increase of BMI.
(p=0.5). But when stratified according to menopausal status, a protective effect was found in postmenopausal women (p=0.078) whereas an increased risk was observed in premenopausal women (p=0.2). A high BMI at age 20 seemed to be associated, but not significantly with an increased risk of ovarian cancer (p=0.72) (Table II).

The case waist measurements were significantly higher than those of the controls (86.5 cm versus 80 cm, p<0.001). The ORs showed an increased risk for women with a waist measurement higher than 80 cm (OR=2.18, 95% CI=1.20-3.96). No difference was reported for hip measurements. The WHR was significantly higher in the cases than in the controls (0.87±0.07 versus 0.81±0.07, p<0.001) (Table I) and the risk of developing ovarian cancer was significantly increased when the WHR was larger than 0.8 (p<10–6) (Table II) and independently of menopausal status (data not shown). No difference was noted concerning anatomopathology (p=0.64) and the grade of the tumor (p=0.44).

The difference in weight gain between age 20 and the present age was smaller in the cases than in the controls (2.2 versus 3.5, p=0.025). Since BMI, BMI at age 20, and hip measurements were similar in the two groups, the women who developed ovarian cancer had a larger waist at age 20. Height was not associated with the risk of ovarian cancer.

A multivariate analysis was performed using the most influential factors brought out by ORs analysis i.e. WHR, OC use, breastfeeding and length of menstrual cycles (Table III). Since receiver operating characteristic (ROC) analysis showed a more discriminant curve for WHR than for waist measurement, WHR was used for the multivariate analysis. WHR was the main risk factor of ovarian cancer. Increased risk was observed with the highest classes of WHR as opposed to the reference group (WHR=0.801-0.85: OR=2.93, 95% CI=1.94-4.42; WHR >0.85: OR=8.58, 95% CI=3.77-19.52). Multivariate analysis confirmed the protective effect of OC, the use of which significantly reduced the risk of ovarian cancer. On the other hand, the length of breastfeeding and menstrual cycles did not significantly modify risk.

**Discussion**

A high WHR was the most relevant risk factor for ovarian cancer, but no association with other anthropometric factors such as BMI and BMI at age 20 was observed. The protective effect of OC use was confirmed. No association was found with other factors, including age at menarche, length of menstrual cycles and breastfeeding.

Studies of the relationship between BMI and the risk of ovarian cancer have been inconclusive, finding either a positive correlation (6-14), no relationship (15-22), or a negative association (23). The present results suggested an interaction with menopausal status, with higher BMI being more associated with ovarian cancer risk in premenopausal women than in postmenopausal women, in agreement with Beehler et al. (24) and with the results of a recent pooled analysis of 12 cohort studies (25). An increased risk of ovarian cancer with BMI was reported in a recent study particularly for women who never used HRT (26). Greer et al. showed a slight increase in risk with weight during adulthood and later in life, which was most apparent among nulliparous women (27). Fairfield et al. did not find any association between recent BMI and risk of ovarian cancer, but reported that a high BMI during early adulthood was associated with an increased risk of premenopausal cancer (17). A case-control study reported an association between ovarian cancer and increased BMI at age 18 and during most of adult life (13), whereas results from the Nurses’ Health Study did not find any relation between ovarian cancer risk and BMI at age 18 or birthweight (28).

A strong relationship between WHR and the risk of ovarian cancer regardless of menopausal status was found in the present study, underscoring the role of central adiposity in the induction of ovarian cancer. Dal Maso et al. reported an OR of 1.45 for the WHR highest quartile (WHR ≥0.89: 95% CI=1.07-1.96 vs. WHR ≤0.76) (16), confirming previous work in which multivariate-adjusted relative risks for the upper three quartiles were 2.0, 1.6, and 2.3 compared to the lower quartile of WHR (29).

Physiopathologically excess weight increases circulating estrogen levels, particularly in postmenopausal women. Estradiol and estrone are known to stimulate cell growth in normal and malignant ovarian surface epithelial cell lines (6). Both estrogen and androgens are synthesized in the ovaries, but the production of androgens seems higher in these
organs. Androgen and progesterone receptors outnumber estrogen receptors in epithelial ovarian cells, suggesting a major role of the former. Progesterone might protect against ovarian cancer. An apoptotic effect of the progesterin component of an oral contraceptive on ovarian epithelium was shown in a study in primates (30). Furthermore, a higher risk for ovarian cancer was found with the use of estrogen-progestin hormone replacement therapy (HRT) versus estrogen-only HRT (31, 32). Plasma estrone is synthesized in adipose tissue by the aromatization of androstenedione that is in turn converted to testosterone in the ovaries (6).

A high WHR is associated with hyperandrogenemia, polycystic ovaries, hyperinsulinemia and insulin resistance, which lead to increased cholesterol and insulin and insulin-like growth factor-1 (IGF-1) levels (2, 33, 34). Obesity is also associated with insulin resistance, resulting in increased ovarian testosterone production (2). IGF is produced in ovaries and the liver (2), and insulin exerts mitogenic and antiapoptotic activities and may play a role in ovarian cancer risk through its effects on the synthesis and metabolism of other hormones (35). Both insulin and IGF enhance ovarian progesterone production in vitro and stimulate aromatase, resulting in increased conversion of androgens to estrogens. Studies have shown that central adiposity was associated with serum levels of ovarian and adrenal androgens (2, 35).

The present results showed that weight gain was lower and waist measurement at age 20 higher in the cases. Dal Maso et al. showed that relatively constant weight during adult life resulted in the persistence of ovulatory cycles (16). One of the major causes of ovarian cancer is the cyclical stimulation of the ovarian epithelium by gonadotrophins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), which is a result of the stimulation by estrogen or estrogen precursors and leads to cell proliferation and malignant transformation.

OC use has been consistently negatively linked to ovarian cancer. La Vecchia showed overall protection of approximately 30% for ever-OC users, this protection increased with the duration of use (5% per year of use to about 50% for more than ten years) and the results were independent of family history (36). For short-term OC use, a decrease in risk was observed in women who had taken OC for less than 6 months and who stopped because of side-effects (OR=0.59, 95% CI=0.40-0.87); decreased risk was also observed in women taking OCs for more than 6 months (independently of their motivation to stop use) (37). When high-estrogen/high-progestin pills were compared to low-estrogen/low-progestin pills, the same decrease in risk was observed, suggesting that protection was independent of the dose of estrogen and progestin and that the pills currently in use are as effective in reducing the risk of ovarian cancer as pills from the previous generation (38).

Fathalla suggested that neoplasia of ovarian epithelium may be due to repeated chronic ovulation without pregnancy and that there was a rapid proliferation of ovarian epithelium during the 24 hours following ovulation (3). Casagrande et al. extended this concept to a decreased risk associated with anovulation due to OC use (39). The proliferation and transformation of the ovarian epithelium may be due to the exposure to estrogen following ovulation (39). The established protective effect of OC use may also be due to the suppression of the LH peak and to a decrease of endogenous estradiol production. If estrogens are related to an increased risk of ovarian cancer, oral contraception might have some protective effect by lowering the overall level of estrogens (40).

To confirm these results, more patients need to be studied. Recall bias particularly weight at age 20, is possible in this type of study, and also other factors such as physical activity were not taken into account in the present study. Few studies have assessed the role of physical activity in the risk of ovarian cancer. Although older studies found that physical activity was an independent risk factor for ovarian cancer (29, 41), later studies did not find an association between physical activity and ovarian cancer (42, 43). Weiderpass et al. investigated the role of physical activity at age 14 and 30 but it did not show protection from ovarian cancer (42).

This study focused on hormonal factors and risk of ovarian cancer. Since ovarian cancer is associated with a high mortality rate, studies must be conducted to determine risk factors and therefore contribute to the prevention of this disease. The present results emphasized the major role of central adiposity in this risk, suggesting the key involvement of androgen conversion within adipose tissue. The protective effect of OC use via the suppression of ovulation was confirmed in our study.

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