Influence of menstrual and reproductive factors on ovarian cancer risk in women with and without family history of breast or ovarian cancer

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Background
As women with a family history of ovarian and/or breast cancer possibly inherit genetic changes that alter their risk of ovarian cancer, other established risk factors for ovarian cancer may influence the risk differently in women with and without a family history of the disease.

Methods
Case-control study conducted between 1983 and 1991 in Northern Italy. Cases were 971 women, under 75 years, with incident, histologically confirmed epithelial ovarian cancer, and controls were 2758 women, under 75 years, admitted to hospitals for non-malignant, non-hormone-related conditions, who had not undergone bilateral oophorectomy. Of these, 93 cases and 139 controls had a family history of ovarian and/or breast cancer.

Results
The risk of ovarian cancer increased with irregular menstrual cycles, late age at menopause, natural menopause, nulliparity, never use of oral contraceptives and use of hormone replacement therapy. We computed an ‘adult life risk score’ (ALRS) considering the combined effect of these factors. Compared to women without a family history and a low ALRS, the OR was 1.7 for women without family history and high ALRS, 1.4 for women with a family history and low ALRS, and 3.5 for women with a family history and high ALRS.

Conclusions
Intervention on selected hormonal risk factors for ovarian cancer might be important for women with a family history of the disease.

Keywords
Breast cancer, case-control study, family history, hormone replacement therapy, menstrual factors, oral contraceptives, ovarian cancer, reproductive factors, risk factors

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risk score’ (ALRS), derived from selected menstrual and reproductive factors. A similar approach had been used for breast cancer.\textsuperscript{17,18}

Materials and Methods

Between 1983 and 1991 we conducted a case-control study of ovarian cancer.\textsuperscript{19,20} Data were collected in the major teaching and general hospitals in the greater Milan area, Northern Italy. The cases were 971 women aged 22–74 years (median 54 years) with histologically confirmed epithelial ovarian cancer, diagnosed less than one year before the interview. Controls were 2758 women aged 23–74 (median 52 years) admitted to the same hospitals for acute conditions not related to gynaecological, hormonal or neoplastic diseases and who had not undergone bilateral oophorectomy. Of these, 34% had traumatic conditions (mostly fractures and sprains), 30% non-traumatic orthopaedic disorders (mostly low back pain and disc disorders), 16% were admitted for acute surgical conditions (mostly abdominal, such as acute appendicitis or strangulated hernia), and 20% for miscellaneous other illnesses, such as eye, ear, nose and throat, and dental disorders. Approximately 4\% of cases and controls approached refused the interview.

The questionnaire included information on personal characteristics and habits, including marital status, education and other socioeconomic indicators, smoking, alcohol and coffee consumption, anthropometric variables, diet, menstrual and reproductive factors (such as age at menarche, menstrual cycles, number of abortions and births, and age at first birth), selected medical conditions, history of benign breast disease, and history of lifelong use of oral contraceptives and hormone replacement therapy. Information on the number of sisters and on ovarian, reproductive factors (such as age at menarche, menstrual cycles, parity, age at first birth), selected medical conditions, history of benign breast disease, and history of lifelong use of oral contraceptives and hormone replacement therapy.

Data analysis

Odds ratios (OR) of ovarian cancer and the corresponding 95% CI were derived using unconditional multiple logistic regression models, fitted by the method of maximum likelihood.\textsuperscript{21} All the regression equations included terms for age in quinquennia and area of residence. An ALRS of ovarian cancer, including regularity of menstrual cycles, age at and type of menopause, parity, use of oral contraceptives and hormone replacement therapy, was calculated by assigning a value of 1 to women at high risk with respect to a particular factor and 0 otherwise, and summing the selected adult life risk factors using weights equal to the excess rate ratio (OR-1).\textsuperscript{17,18} Thus, for example, a women with regular menstrual cycle, aged 47 years at menopause, with surgical menopause, with one child, and who has never used oral contraceptives and is using hormone replacement therapy, will have a score equal to: \[ \text{ALRS} = (2.1 - 1) + (1.4 - 1) + 0 + 0 + (1.2 - 1) + (1.8 - 1) = 2.4. \] The ALRS was divided into tertiles (the upper cutoff points of the first and second tertiles were 2.19 and 2.42, respectively), and the lowest score was compared to the two higher scores taken together.

Results

Ninety-three (9.6\%) ovarian cancer cases and 139 (5.0\%) controls reported a family history of breast and/or ovarian cancer, corresponding to a multivariate OR of 2.0 (95\% CI: 1.4–2.6). Table 1 shows the distribution of cases and controls and the corresponding OR, according to age and selected menstrual and reproductive factors, and the use of exogenous hormones in women with and without a family history of breast and/or ovarian cancer. The risk of ovarian cancer increased with regular menstrual cycles, late age at menopause, natural (versus surgical) menopause, nulliparity, never use of oral contraceptives and ever use of hormone replacement therapy in women with and without a family history. The OR were not significantly heterogeneous across the family history groups.

The distribution and the OR for ovarian cancer by family history of ovarian and/or breast cancer and ALRS are shown in Table 2. Compared with women with no history and a low ALRS, the OR was 1.7 for those with no family history and high ALRS, 1.4 for women with a family history and a low ALRS, and 3.5 for women with a family history and a high ALRS.

Discussion

This study suggests that a family history of ovarian and/or breast cancer was associated with a moderate increase in ovarian cancer risk (OR = 1.4) when the ALRS was low. The excess risk became substantial when both a positive family history and selected environmental factors (high ALRS) were present (OR = 3.5).

For most risk factors considered our risk estimates are in agreement with the overall epidemiological evidence on ovarian cancer.\textsuperscript{5,11–14} The strength of the association of various hormonal factors with ovarian cancer risk was similar in women with and without a family history of the disease, similarly to the findings of a French Canadian case-control study.\textsuperscript{16} The definition of a composite value of a family propensity and environmental risk factors allows a better quantification of the risk factors and may suggest preventive priorities.

A limitation of this study is that genetic susceptibility was evaluated indirectly on the basis of a family history of ovarian and/or breast cancer in first-degree relatives; consequently, the group with a family history includes women with various genetic risk profiles. The ALRS may be criticized since it is a simple sum of risk factors with different biological and aetiological mechanisms. Further, some of the risk factors included in the ALRS (e.g. menstrual cycle pattern and age at menopause) may themselves be correlated to some genetic characteristics influencing ovarian cancer risk.

Although this study was not population-based, cases were identified in the major teaching and general hospitals of the area under surveillance, the controls came from comparable catchment areas, the participation of cases and controls was almost complete, and the hospital-based design may improve the comparability of recall of several covariates by cases and controls.\textsuperscript{17,18} The comparison group only included acute conditions unrelated to gynaecological conditions and other recognized risk factors for ovarian cancer. We collected information only about first-degree relatives (mother and sisters), thus reducing the difference between cases and controls in recall bias for history of ovarian and/or breast cancer in their family.

In conclusion, in a preventive and public health perspective, our findings—related to a few selected and partly modifiable risk factors—underscore the importance and the scope for
intervention and prevention of ovarian cancer in women with a family history of ovarian and/or breast cancer. This may include chemoprevention by combined oral contraceptives and selective screening for the disease, although effective screening procedures specific for ovarian cancer have not been identified yet.

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References


