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Family history of cancer and risk of ovarian cancer

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Abstract

The aim of this study was to examine the relationship between history of cancer in first-degree relatives and ovarian cancer risk. Between 1992 and 1999, we conducted a case–control study in Italy on 1031 women with epithelial ovarian cancer and 2411 women admitted to hospital for acute non-neoplastic conditions. Odds ratios (OR) were estimated using unconditional logistic regression, adjusted for age and several potential confounders. Overall, 27 cases and nine controls reported a family history of ovarian cancer (OR = 7.0; 95% confidence interval (CI) 3.1–16). The OR was 23 (95% CI 2.6–212) below age 50 years, based on 10 cases and one control only. The risk of ovarian cancer was also increased in women with a family history of cancer of the stomach (OR = 1.5; 95% CI 1.0–2.1), intestine (OR = 1.7; 95% CI 1.2–2.4), lung (OR = 1.3; 95% CI 1.0–1.8), breast (OR = 2.3; 95% CI 1.7–3.1), lymphomas (OR = 2.3; 95% CI 1.0–5.1) and all sites (OR = 1.6; 95% CI 1.4–1.9). Our results confirm the higher ovarian cancer risk in women with a family history of ovarian and breast cancer, and suggest a few associations with other sites.

Keywords: Case–control study, Epidemiology, Family characteristics, Ovarian cancer

1. Introduction

Women with a family history of ovarian cancer are at a higher risk of developing ovarian cancer [1]. This has been interpreted as a hereditary susceptibility genetically transmitted across generations [2]. Multiple cases of cancers of the ovary and breast in the same family have also been observed.

Two tumour-suppressor genes have been identified, *BRCA1* on chromosome 17q and *BRCA2* on chromosome 13q, whose autosomal dominant transmitted mutations confer a high risk of breast and ovarian cancers [3,4].

Ford and colleagues [5] estimated that the gene frequency of *BRCA1* was 0.0006 in two population-based genetic epidemiological studies from England and Wales, and that the proportion of ovarian cancer cases due to *BRCA1* was 5.7% below age 40 years, 4.6% between 40 and 49 years and 2.1% between 50 and 70 years.

An excess of ovarian cancer has also been observed in families affected by Lynch syndrome 2, a form of the hereditary non-polyposis colorectal cancer (HNPCC) syndrome, which carries a very high risk of colorectal cancer, but also excesses of cancers of the endometrium, ovary, small intestine, urinary tract, hepatobiliary system, stomach and pancreas [6]. Five different mismatch repair genes have so far been identified, whose mutations lead to HNPCC [7].

It is not clear whether these genes completely account for familial ovarian cancer, or whether other genes exist, for which some alleles imply a higher risk for ovarian cancer than others [8,9].

The risk of ovarian cancer also appears higher in women with a family history of cancers other than

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ovary and breast, e.g. stomach, colorectal and pancreas cancers [10–20].

Given the differences in the genetic background of various populations, it is important to study the familial risk of ovarian cancer in different populations. Italy may differ from populations of North European or Jewish ancestry, where most investigations have been conducted.

We analysed data from a uniquely large case–control study conducted in four Italian areas, including information on history of any type of cancer in first-degree relatives.

2. Patients and methods

A case–control study of epithelial ovarian cancer was conducted between January 1992 and September 1999 in four Italian areas: greater Milan, the provinces of Pordenone, Padua and Gorizia (north-eastern Italy); the province of Latina (central Italy); the urban area of Naples (southern Italy). The interviewers were centrally trained. Less than 4% of cases and controls approached refused to be interviewed, and the response rates did not vary across hospitals and geographical areas.

Cases were 1031 women (median age 56 years, range 18–79 years) with incident (i.e. diagnosed within a year before the interview), histologically-confirmed epithelial ovarian cancer, admitted to the major teaching and general hospitals in the areas under surveillance. The histological type was serous in 493 cases (48%), mucinous in 81 (8%), endometrioid in 78 (8%), other in 98 (10%) and unspecified in 281 (27%).

Controls were 2411 women (median age 57 years, range 17–79 years) residing in the same geographical areas and admitted to the same network of hospitals as the cases, for a wide spectrum of acute conditions unrelated to known or potential risk factors for ovarian cancer. Women were specifically excluded if admitted for hormonal and gynaecological diseases, and if they had undergone ovariectomy. Among controls, 26% had traumatic conditions (mostly fractures and sprains), 28% non-traumatic orthopedic disorders (mostly low back pain and disc disorders), 15% acute surgical conditions (mostly abdominal, such as acute appendicitis or strangulated hernia), and 31% miscellaneous other illnesses (such as eye, ear, nose and throat or dental disorders).

All interviews were conducted in hospital using a structured questionnaire which included information on personal characteristics and habits, education and other socio-economic factors, general lifestyle habits, such as smoking, alcohol and coffee consumption, a validated food frequency section, physical activity, menstrual and reproductive history, selected medical conditions, and history of lifetime use of aspirin and hormone preparations. The subjects were specifically asked how many sisters and brothers they had, and whether their parents, siblings, children, grandparents or spouse had ever had cancer (excluding non-melanomatous skin cancer). For each relative with a history of cancer, the vital status at the time of interview, the current age or the age at death, the site of the tumour and the age at diagnosis were recorded. In the present analysis, we considered the history of cancer in first-degree relatives only, i.e. parents, siblings and children. On account of recall and classification difficulties, some sites were combined (i.e. the whole intestinal tract, Hodgkin's and non-Hodgkin lymphomas, cervix and corpus uteri).

2.1. Statistical analysis

We estimated the odds ratio (OR) of ovarian cancer according to history of cancer of selected sites in first-degree relatives using unconditional multiple logistic regression models [21]. The models included terms for age (quinquennia), study centre, years of education, parity, oral contraceptive use, and number of siblings, brothers or sisters, depending on the cancer site.

3. Results

Table 1 gives the distribution of ovarian cancer cases and the comparison group according to age, education and number of sisters and brothers. Cases tended to be

Table 1
Distribution of 1031 cases of ovarian cancer and 2411 controls according to selected variables, Italy, 1992–1999

Variable	Cases No. (%)	Controls No. (%)
Age (years)		
<30	31 (3.0)	63 (2.6)
30–39	68 (6.6)	178 (7.4)
40–49	198 (19.2)	479 (19.9)
50–59	341 (33.1)	694 (28.8)
60–69	316 (30.6)	737 (30.6)
⩾70	77 (7.5)	260 (10.8)
Years of education[a]		
<7	570 (55.7)	1417 (59.4)
7–11	227 (22.2)	620 (26.0)
⩾12	227 (22.2)	349 (14.6)
Number of sisters[a]		
0	256 (24.9)	589 (24.4)
1	311 (30.2)	678 (28.1)
2	194 (18.8)	477 (19.8)
⩾3	269 (26.1)	665 (27.6)
Number of brothers[a]		
0	217 (21.1)	511 (21.2)
1	330 (32.0)	749 (31.1)
2	227 (22.0)	515 (21.4)
⩾3	256 (24.9)	634 (26.3)

[a] The sum does not add up to the total because of some missing values.

more educated than controls, but no difference emerged in the number of sisters or brothers. Table 2 shows the ORs of ovarian cancer in relation to history of selected cancers in first-degree relatives overall and in two age groups. A total of 27 cases and nine controls reported a family history of ovarian cancer, and the corresponding OR was 7.0 (95% confidence interval (CI) 3.1–16). The OR was 23 (95% CI 2.6–212) in women below age 50 years, but this estimate was based on 10 cases and one control only. Other significant associations were observed for women reporting a family history of cancer of the stomach (OR = 1.5; 95% CI 1.0–2.1), intestine (OR = 1.7; 95% CI 1.2–2.4), lung (OR = 1.3; 95% CI 1.0–1.8), breast (OR = 2.3; 95% CI 1.7–3.1) and lymphomas (OR = 2.3; 95% CI 1.0–5.1). The OR was 1.6 (95% CI 1.4–1.9). for all cancer sites combined, and 1.4 (95% CI 1.2–1.7) for all sites except breast and ovary. The OR was higher below age 50 years for lymphomas, above age 50 years for breast, and no clear differences emerged for the other sites.

Table 3 shows the OR of ovarian cancer according to selected aspects of family history of the same neoplasm. Compared with women who did not report a family history, those with one affected relative had an OR of 6.8 (95% CI, 2.9–16), while only two cases and no controls reported two affected relatives. No notable differences emerged according to the type of relative, while the risk was higher—although not significantly—when the relative was diagnosed at a younger age. When the different histological types were analysed separately, a family history was reported by 14 cases with serous ovarian cancer (OR = 6.9, 95% CI 2.5–19), 0 with mucinous, 3 with endometrioid (OR = 13, 95% CI 2.0–81), 4 with other specified ovarian cancer (OR = 22, 95% CI 5.9–80) and 6 with ovarian cancer of unspecified histology (OR = 4.9, 95% CI 1.5–16).

Table 4 presents the OR of ovarian cancer in relation to selected aspects of family history of breast, intestinal and stomach cancer. The OR of ovarian cancer for women reporting a family history of breast cancer were 2.5 and 0.8 for one and two or more affected relatives, respectively. The corresponding figures were 1.6 and 3.2 for intestinal cancer, and 1.5 and 2.1 for stomach cancer. No clear pattern emerged when the age of the relative at diagnosis of ovarian cancer was considered.

4. Discussion

This study confirms that a family history of ovarian cancer in first-degree relatives increases the risk of ovarian cancer. A family history of a few other cancer sites, including breast, intestine, stomach and lymphomas, was also directly associated with ovarian cancer risk, and the OR was increased for family history of any cancer.

Table 2
Odds ratio of ovarian cancer according to family history of selected cancers in first-degree relatives in strata of age of the proband and in the overall dataset: Italy, 1992–1999

Cancer site	Age < 50 years			Age ⩾ 50 years			All subjects
	Cases	Controls	OR[a] (95% CI)[b]	Cases	Controls	OR[a] (95% CI)[b]	OR[a] (95% CI)[b]
Oral cavity	3	10	0.9 (0.3–3.8)	14	22	1.6 (0.8–3.3)	1.5 (0.8–2.8)
Oesophagus	1	6	0.3 (0.03–2.6)	5	11	1.3 (0.4–3.9)	0.8 (0.4–2.2)
Stomach	17	26	1.8 (0.9–3.6)	45	83	1.4 (0.9–2.1)	1.5 (1.0–2.1)
Intestines	8	18	1.2 (0.5–3.2)	52	71	1.8 (1.2–2.7)	1.7 (1.2–2.4)
Liver	7	14	1.3 (0.5–3.5)	37	75	1.5 (0.9–2.3)	1.4 (0.9–2.1)
Pancreas	5	5	2.0 (0.5–7.9)	16	32	1.2 (0.6–2.3)	1.3 (0.7–2.4)
Larynx	6	11	2.2 (0.7–7.4)	18	31	1.3 (0.7–2.4)	1.5 (0.8–2.6)
Lung	18	40	1.4 (0.7–2.6)	63	128	1.3 (0.9–1.8)	1.3 (1.0–1.8)
Breast	21	30	1.4 (0.7–2.5)	83	81	2.8 (1.9–3.9)	2.3 (1.7–3.1)
Uterus, cervix and corpus	5	17	0.6 (0.2–1.9)	26	35	1.3 (0.8–2.3)	1.2 (0.7–1.9)
Ovary	10	1	23 (2.6–212)	17	8	5.6 (2.2–14)	7.0 (3.1–16)
Prostate	5	14	0.9 (0.3–2.6)	12	21	1.3 (0.6–2.9)	1.1 (0.6–2.1)
Bladder	3	11	0.9 (0.2–3.4)	7	18	0.8 (0.3–2.0)	0.8 (0.4–1.7)
Kidney	4	3	2.0 (0.4–11)	4	9	0.8 (0.2–2.8)	1.2 (0.4–3.0)
Brain	3	7	1.1 (0.3–4.5)	10	29	0.8 (0.4–1.8)	0.9 (0.4–1.7)
Thyroid	1	1	0.9 (0.05–17)	3	4	0.8 (0.2–4.1)	0.9 (0.2–3.6)
Lymphomas	7	5	4.5 (1.3–16)	5	11	1.3 (0.4–4.1)	2.3 (1.0–5.1)
Leukaemias	5	11	1.2 (0.4–3.8)	14	26	1.6 (0.8–3.2)	1.4 (0.8–2.6)
Other or unspecified	12	27	1.2 (0.6–2.7)	29	67	1.1 (0.7–1.7)	1.1 (0.8–1.7)
All sites	116	224	1.4 (1.0–2.0)	353	628	1.7 (1.4–2.1)	1.6 (1.4–1.9)
All sites except ovary and breast	85	193	1.3 (0.9–1.9)	255	539	1.4 (1.1–1.7)	1.4 (1.2–1.7)

[a] Odds ratios estimated from multiple logistic regression models including terms for age, study centre, education, parity, oral contraceptive use and number of siblings, brothers or sisters, depending on the cancer site.
[b] 95% confidence intervals (CI) are given in parentheses.

Table 3
Odds ratio of ovarian cancer according to selected aspects of family history of ovarian cancer in first-degree relatives: Italy, 1992–1999

	No. cases	No. controls	OR[a] (95% CI)[b]
No family history	1004	2402	1[c]
No. of affected relatives			
1	25	9	6.8 (2.9–16)
⩾2	2	0	∞
Youngest age at diagnosis in relatives (years)			
<50	8	1	13 (1.5–112)
⩾50	19	8	6.2 (2.5–16)
Relative affected			
Mother	13	5	6.5 (2.1–20)
Sister	13	4	7.7 (2.3–26)
Mother and sister	1	0	∞

[a] Odds ratio estimated from multiple logistic regression models including terms for age, study centre, education, parity, oral contraceptive use and number of sisters.
[b] 95% confidence intervals (CI) are given in parentheses.
[c] Reference category.

Table 4
Odds ratio of ovarian cancer according to selected aspects of family history of breast, intestinal and stomach cancer in first-degree relatives: Italy, 1992–1999

	Breast cancer			Intestinal cancer			Stomach cancer		
	No. cases	No. controls	OR[a] (95% CI)[b]	No. cases	No. controls	OR[a] (95% CI)[b]	No. cases	No. controls	OR[a] (95% CI)[b]
No family history	927	2300	1[c]	971	2322	1[c]	969	2302	1[c]
Number of affected relatives									
1	100	99	2.5 (1.8–3.4)	57	86	1.6 (1.1–2.3)	58	104	1.5 (1.0–2.1)
⩾2	4	12	0.8 (0.2–2.6)	3	3	3.2 (0.6–17)	4	5	2.1 (0.5–8.6)
Youngest age at diagnosis in relatives, years[d]									
<50	43	39	2.5 (1.5–4.0)	10	13	2.1 (0.9–5.3)	4	12	1.0 (0.3–3.4)
⩾50	58	70	2.1 (1.4–3.1)	46	75	1.5 (1.0–2.3)	55	91	1.6 (1.1–2.3)

[a] Odds ratio estimated from multiple logistic regression models including terms for age, study centre, education, parity, oral contraceptive use and number of siblings or sisters (for breast).
[b] 95% confidence intervals (CI) are given in parentheses.
[c] Reference category.
[d] The sum does not add up to the total because of some missing values.

This study is based on information provided by the subjects, and some inaccuracy in reporting cancer in first-degree relatives is conceivable. Moreover, cases may recall family history of cancer better than controls. Two studies from Canada, one on breast [22] and one on ovarian cancer [10], evaluated the accuracy of reporting family history of cancer in cases and controls, and found satisfactory results for first-degree relatives, but less accurate reporting for second-degree relatives. A study from Finland on breast cancer patients also found accurate reporting of family history of cancer in first-degree relatives [23], while another, from Utah, on colon cancer patients and their controls found less consistent results, particularly for some cancer sites, including cancers of the reproductive tract [24]. Given the lower accuracy of cancer reporting in second-degree relatives, we limited our analysis to first-degree relatives.

Although the use of hospital controls has long been debated [21], we carefully excluded any diagnosis for controls potentially related to ovarian cancer. Moreover, hospital admission is unlikely to be related to the same genetic aspects as familial ovarian cancer, the hospital setting itself may have improved the comparability of information on medical history [25], participation was practically complete, and the catchment areas of cases and controls were comparable.

Our findings of an elevated risk of ovarian cancer in subjects with a family history of cancer at the same site are in broad agreement with other reports, although our point estimate is somewhat higher than in other studies. Given the broad confidence interval due to the small

number of subjects reporting a family history of ovarian cancer, our results none the less do not contrast with the common OR of 3.1 (95% CI 2.6–3.7) estimated from a meta-analysis of published studies [1], which became 4.0 when only case–control studies were considered. Possible explanations for the higher OR in our study include, besides chance, a difference in the population studied or a more marked differential recall in this population. In a previous case–control study on ovarian cancer in the same population the OR was 2.6 [26], so chance is the most likely explanation for the present finding. In fact, the combined OR of these two studies is 4.0, similar to that reported by Stratton and colleagues [1].

The OR of 23 below age 50 years (proband's age) is based on only 10 cases and one control, and the lower confidence interval is 2.6, compatible with the overall risk. The OR was also higher when the age at diagnosis of the relative was below 50 years, but this estimate was also based on small numbers. In other studies, no consistent pattern of risk emerged when either the proband or the relative was younger at the onset of ovarian cancer [1].

No clear difference emerged in our study when the affected relative was the mother or a sister. In their meta-analysis, Stratton and colleagues [1] found comparable risks associated with an affected sister or mother, but women with an affected daughter were at a lower risk. This is difficult to explain in terms of a genetic model. The three estimates, however, were based on different studies.

Only two cases and no control reported more than one first-degree relative with ovarian cancer. This is consistent with the higher risk estimated in previous studies [1].

The major strength and originality of this study is that the information was systematically collected on history of cancer at various sites in relatives, meaning that quantitative estimates of ovarian cancer risk could be made with reference to family aggregation of other cancers. We found a number of direct associations, and differential reporting by cases and controls cannot be ruled out. However, most of them have also been reported in other studies.

The OR of 2.3 in women with a history of breast cancer in first-degree relatives is slightly higher than in most studies, ranging between 1.3 and 1.8 [10–12,14,16,18–20,27]. No clear pattern emerged according to age at diagnosis, although some studies found a stronger risk at a younger age [12].

Small increases in the risk of ovarian cancer have also been associated with a family history of cancer of the stomach, intestines, pancreas and uterus in some, although not all, studies [10–20,27]. The OPCS study investigated mortality among 4111 first-degree relatives of 1188 women diagnosed with ovarian cancer between 1954 and 1981 in England and Wales [16] and found significant excesses of cancers of the stomach (69 observed cases versus 47 expected on the basis of national rates, standardised mortality ratio, SMR, 146), ovary (35 observed versus 18 expected, SMR = 223) and all neoplasms combined (574 observed versus 476 expected, SMR = 121). Non-significant excesses were found for colorectal cancer (80 observed versus 59 expected, SMR = 136), pancreatic cancer (26 observed versus 22 expected, SMR = 134) and breast cancer (60 observed versus 47 expected, SMR = 128). If the increase in ovarian cancer risk associated with family history of some neoplasms like stomach and colorectal cancer is real, but small, it is conceivable that not all studies will find an association. The possibility that abdominal cancers may have been misreported or even misdiagnosed cannot be ruled out. However, given the much lower frequency of ovarian cancer compared with other abdominal cancers, it is unlikely that all the excesses observed are attributed to misreported/misdiagnosed cases of ovarian cancer.

We found a 40% higher risk of ovarian cancer in patients reporting a history of cancer at any site, excluding breast and ovary. There may have been some general over-reporting of cancer history in the families of cases. However, in a companion study on breast cancer [28] using the same design, study areas and questionnaire, and with partially overlapping controls, the risk of breast cancer associated with family history of cancer at any site excluding breast was close to unity, and there is no clear reason why ovarian cancer cases should over-report cancer in relatives more than breast cancer cases. Since in hereditary syndromes involving ovarian cancer, like HNPCC, an excess of a variety of other cancers has also been reported, the weak increase in risk may be real.

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