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Risk factors for ovarian cancer histotypes

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ABSTRACT

To analyse the risk factors for different histologic types of ovarian cancer, we conducted a case-control study. The cases included 750 women with incident, histologically confirmed invasive epithelial ovarian cancer subdivided into: 493 serous, 81 mucinous, 78 endometrioid, and 98 other histologies. The controls included 2411 women admitted to the same hospitals as cases. The odds ratios for women with three or more births, in comparison with nulliparae, were 0.6 for serous, 0.4 for endometrioid, 1.0 for mucinous and 0.7 for other histological types of ovarian cancer. Family history of ovarian/breast cancer was associated to the risk of all ovarian cancer types, except mucinous ones. Selected dietary factors were less strongly directly (meat and starch), or inversely (fish and vitamin E) related to mucinous than to other histological types of ovarian cancer. High occupational physical activity was inversely related to the risk of ovarian cancer, with no heterogeneity across histologies. In conclusion, the association of reproductive factors and of selected dietary habits was weaker for mucinous ovarian cancer than for other histologic types.

1. Introduction

Epithelial cancers account for about 90% of ovarian cancers. They include four major histologic types: serous (the most common subtype, accounting for about 50% of all epithelial ovarian cancers), mucinous, endometrioid, clear cell and other less common types.[1]

The potentially different impact of risk factors for ovarian cancer on different histotypes of the disease has not been adequately investigated. Some evidence showed that mucinous ovarian cancer may in some aspects differ from other histotypes[2–4]: a protective role for reproductive factors was found for serous and other non-mucinous ovarian cancers, but less consistently for mucinous ones. However, other studies did not show any difference.[5–7] In a paper on this issue, based on a previous Italian dataset, parity and oral contraceptive (OC) use were inversely related to the risk of serous and endometrioid, but not of mucinous ovarian cancer.[8]

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In this report, we consider the relationship between selected risk factors for ovarian cancer and the risk of different histologic types of the disease, examining data from a multicentre study conducted in Italy, which is based on a large dataset and includes detailed information on several variables as compared to previous work.[8]

2. Materials and methods

The data were derived from a case-control study of ovarian cancer, conducted between January 1992 and September 1999 in four Italian areas: the Greater Milan, the provinces of Pordenone, Gorizia and Padua in northern Italy; the province of Latina in central Italy; and the urban area of Naples in southern Italy.[9,10] Cases included 1031 women (median age 56 years, range 18–79) with incident, histologically confirmed invasive epithelial ovarian cancer, diagnosed within 1 year before the interview, and with no previous diagnosis of cancer. They were grouped into four histologic categories: serous ($n = 493$), mucinous ($n = 81$), endometrioid tumours ($n = 78$) and others histologies, including clear cell and undifferentiated epithelial tumours ($n = 98$). We were unable to perform an independent review of pathological material. Consequently, we excluded from the analyses 281 (27.3%) cases, whose information on hystologic type was not available in the medical records at the time of interview, and considered the remaining 750 cases.

Controls included 2411 women (median age 57, range 17–79 years) from the same geographic areas, who were admitted to the same network of hospitals as cases for a wide spectrum of acute conditions, unrelated to known risk factors for ovarian cancer. Women were excluded if they had undergone bilateral oophorectomy and if they had been admitted to hospital for hormonal, gynaecologic diseases, neoplastic conditions, or any chronic disease which may have been caused by long-term lifestyle or diet modifications. Among the controls, 26% had traumatic conditions, 28% non-traumatic orthopaedic disorders, such as low back pain and disc disorders, 15% acute surgical conditions, and 31% miscellaneous other illnesses, such as eye, ear, nose and throat, or dental disorders. Less than 4% of cases and controls approached refused the interview, and the response rates did not vary across hospitals and geographic areas.

All interviews were conducted in hospital using a structured questionnaire, which included information on general characteristics and lifestyle habits, socio-demographic factors, physical activity, history of cancer in first-degree relatives, menstrual and reproductive factors, history of selected medical and surgical conditions and of use of OC and hormone replacement therapy (HRT). The section on physical activity included questions on self-reported intensity of activity at work and during leisure time, separately. Interviewers asked how patients would describe their level of occupational physical activity at age 30–39 years. In particular, patients were asked whether their jobs were 'very heavy–heavy', 'average', 'standing' or 'mainly sitting' according to a structured scale classified into four categories (scores between 1 and 4). For housewives, the work activity score was 3 when they reported doing housework regularly.

An interviewer-administered food-frequency questionnaire (FFQ) was utilised to assess the usual diet during the 2 years preceding diagnosis or hospital admission (for the controls).[11,12] The intake of macro- and micronutrients was estimated using Italian food composition databases, integrated with other published data, when needed.[13] Only selected indicators of diet, and of physical activity, which were related to ovarian cancer risk in the overall dataset,[9,10,14,15] were included in the present histology-specific analyses.

2.1. Data analysis

Odds ratios (OR) of ovarian cancer, and the corresponding 95% confidence intervals (CI), were derived from unconditional multiple logistic regression models, fitted by the method of maximum likelihood.[16] The models included terms for quinquennia of age, study centre and in turn, education, parity, OC, and family history of ovarian/breast cancer in first-degree relatives.

3. Results

Table 1 shows the distribution of cases and controls according to age, education and selected hormonal and reproductive risk factors for ovarian cancer. The corresponding ORs are shown in Table 2. More educated women had about a 2-fold increased risk of ovarian cancer compared with less educated ones for all histologies. Late age at menarche and earlier age at menopause tend to be associated (thought not significantly) with a decreased risk of serous, mucinous and endometrioid, but not of other histotypes. An increasing number of births was inversely associated with the risk of serous and endometrioid, but not of mucinous and other histologies. No association emerged between history of abortion and any of the histological types of ovarian cancer. Family history of ovarian/breast cancer increased the risk of all ovarian cancer types, except mucinous ones. The OR for OC use were below unity for mucinous (OR = 0.6 for $\geqslant$25 months versus never users), endometrioid (OR = 0.7), and other histologies (OR = 0.7), but not for serous ones (OR = 1.1). These findings, however, were not heterogenous across histologies. The OR for HRT use were 1.3 for mucinous, 1.2 for endometrioid, 1.5 for other histologies, and 1.0 for serous, again not significantly heterogenous. The risk of all histotypes was inversely associated with occupational physical activity. The OR for the highest level of activity compared to the lowest one at age 30–39 years were 0.7 for serous, 0.5 for mucinous and endometrioid and 0.6 for other histologies. No significant association was found with leisure time physical activity.

The ORs of different histotypes of ovarian cancer according to selected dietary habits are shown in Table 3. Meat consumption was directly related, and fish consumption inversely related to the risk of ovarian cancer of all histologies, with the exception of mucinous tumour. Starch intake increased the risk of all histologic types (OR = 1.4 for serous and endometrioid, OR = 1.2 for other histologies) except mucinous ones (OR = 0.8). Likewise, vitamin E appeared to be protective for all histotypes (OR = 0.6 for serous, OR = 0.8 for endometrioid, and for other histologies), except for mucinous ones (OR = 1.0).

Table 1 – Distribution of 750 cases of ovarian cancer and 2411 controls according to histologic types, age and selected characteristics (Italy 1992–1999)[a]

	Histologic types								Controls	
	Serous (n = 493)		Mucinous (n = 81)		Endometrioid (n = 78)		Other (n = 98)		(n = 2411)	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Age (years)										
Mean ± SD	55.2 ± 11.5		50.6 ± 12.7		54.6 ± 11.7		54.2 ± 11.6		55.4 ± 11.8	
Range	(18–79)		(18–74)		(18–79)		(18–79)		(17–79)	
⩽44	85	17.2	27	33.3	21	26.9	18	18.4	443	18.4
45–54	140	28.4	17	21.0	25	32.1	24	24.5	615	25.5
55–64	143	29.0	27	33.3	21	26.9	37	37.8	724	30.0
⩾65	125	25.4	10	12.4	11	14.1	19	19.4	629	26.1
Education (years)										
⩽6	266	54.3	42	51.9	44	57.1	55	56.1	1417	59.4
7–11	111	22.7	17	21.0	13	16.9	26	26.5	620	26.0
⩾12	113	23.1	22	27.2	20	26.0	17	17.4	349	14.6
Age at menarche (years)										
⩽12	211	42.9	32	39.5	42	53.9	42	53.9	1003	41.7
13–14	218	44.3	43	53.1	30	38.5	30	38.5	1022	42.5
⩾15	63	12.8	6	7.4	6	7.7	6	7.7	378	15.7
Age at menopause (years)[b]										
⩽44	37	11.3	6	13.6	6	15.4	11	16.4	271	17.0
45–52	222	67.9	25	56.8	25	64.1	44	65.7	964	60.4
⩾53	68	20.8	13	29.6	8	20.5	12	17.9	360	22.6
Parity										
0	86	17.4	13	16.1	14	18.0	17	17.4	381	15.8
1–2	269	54.6	44	54.3	49	62.8	53	54.1	1267	52.6
⩾3	138	28.0	24	29.6	15	19.2	28	28.6	763	31.7
Spontaneous abortions										
0	379	76.9	65	80.3	59	75.6	80	81.6	1831	75.9
⩾1	114	23.1	16	19.8	19	24.4	18	18.4	580	24.1
Family history of ovarian/breast cancer										
No	422	85.6	77	95.1	70	89.7	86	87.8	2291	95.0
Yes	71	14.4	4	4.9	8	10.3	12	12.2	120	5.0
Oral contraceptive use (months)										
Never	430	87.4	74	91.4	70	89.7	88	89.8	2142	89.0
⩽24	37	7.5	4	4.9	4	5.1	7	7.1	143	5.9
⩾25	25	5.1	3	3.7	4	5.1	3	3.1	121	5.0
Hormone replacement therapy use										
Never	464	94.1	76	93.8	73	93.6	90	91.8	2260	93.7
Ever	29	5.9	5	6.2	5	6.2	8	8.2	151	6.3
Occupational physical activity at age 30–39[c]										
1 (lowest)	56	11.7	8	10.7	8	10.4	12	12.6	251	10.7
2	98	20.6	17	22.7	19	24.7	22	23.2	426	18.2
3	230	48.2	39	52.0	39	50.7	44	46.3	1237	52.9
4 (highest)	93	19.5	11	14.7	11	14.3	17	17.9	426	18.2

a In some cases the sum does not add up to the total because of missing values.
b Post-menopausal women only.
c Only subjects aged ⩾30 years at interview.

4. Discussion

The histological distribution of ovarian cancer observed in the study is consistent with published data.[17,18] However, information on histologic types was missing for about 27% of cases. Nevertheless, this is unlikely to cause substantial bias, since the lack of information regarding histology was generally due to the non availability of this data in the medical records. During data collection, histologic type was not known to the interviewers, and the potential different effect of risk factors on different histologic types was unclear. With regard to other potential sources of bias, selection should not have markedly influenced these findings, since cases and controls were identified in hospitals covering comparable catchment areas, participation was almost complete, and women with chronic, gynaecological or hormonal conditions were ex-

Table 2 – Odds ratios (OR) of ovarian cancer and corresponding 95% confidence intervals (CI) according to histologic types and selected factors (Italy, 1992–1999)

	Histologic Types							
	Serous (n = 493)		Mucinous (n = 81)		Endometrioid (n = 78)		Other (n = 98)	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Education (years)								
⩽6	1[a]		1[a]		1[a]		1[a]	
7–11	1.3	1.0–1.7	1.0	0.5–1.9	0.7	0.4–1.4	1.3	0.8–2.1
⩾12	2.2	1.6–3.0	2.3	1.2–4.3	2.1	1.1–4.0	1.4	0.8–2.7
Age at menarche (years)								
⩽12	1[a]		1[a]		1[a]		1[a]	
13–14	0.9	0.7–1.2	1.4	0.8–2.2	0.7	0.4–1.2	0.8	0.5–1.3
⩾15	0.7	0.5–1.0	0.5	0.2–1.3	0.4	0.2–1.1	0.9	0.5–1.7
Age at menopause (years)[b]								
⩽44	0.6	0.4–0.9	0.7	0.2–1.9	0.8	0.3–2.1	0.9	0.5–1.9
45–52	1[a]		1[a]		1[a]		1[a]	
⩾53	0.9	0.6–1.2	1.8	0.8–3.7	0.9	0.4–2.1	0.7	0.4–1.4
Parity								
0	1[a]		1[a]		1[a]		1[a]	
1–2	1.1	0.8–1.5	1.5	0.8–2.9	1.1	0.6–2.2	1.1	0.6–2.0
⩾3	0.6	0.5–0.9	1.0	0.5–2.2	0.4	0.2–0.9	0.7	0.3–1.3
Spontaneous abortions								
0	1[a]		1[a]		1[a]		1[a]	
⩾1	1.0	0.8–1.3	0.8	0.5–1.5	1.1	0.7–2.0	0.7	0.4–1.3
Family history of ovarian/breast cancer								
No	1[a]		1[a]		1[a]		1[a]	
Yes	2.7	1.9–3.9	1.0	0.3–2.8	1.8	0.8–4.2	2.6	1.4–5.0
Oral contraceptive use (months)								
Never	1[a]		1[a]		1[a]		1[a]	
⩽24	1.2	0.8–1.8	0.5	0.2–1.6	0.7	0.2–2.1	1.1	0.5–2.5
⩾25	1.1	0.7–1.8	0.6	0.2–2.0	0.7	0.2–2.5	0.7	0.2–2.4
Hormone replacement therapy use								
Never	1[a]		1[a]		1[a]		1[a]	
Ever	1.0	0.6–1.6	1.3	0.5–3.4	1.2	0.5–3.2	1.5	0.7–3.2
Occupational physical activity at age 30–39[c]								
1 (lowest)	1[a]		1[a]		1[a]		1[a]	
2	0.8	0.5–1.2	0.8	0.3–2.0	0.8	0.3–2.0	0.8	0.4–1.7
3	0.6	0.4–0.9	0.7	0.3–1.6	0.6	0.3–1.5	0.5	0.3–1.1
4 (highest)	0.7	0.4–1.1	0.5	0.2–1.4	0.5	0.2–1.4	0.6	0.2–1.4

OR = Odds ratio. Multivariate estimates including terms for age, study centre and in turn, education, parity, oral contraceptive use, family history of ovarian and/or breast cancer in first degree relatives.

a Reference category.

b Post-menopausal women only.

c Only subjects aged ⩾30 years at interview.

cluded from the study. The reproducibility and reliability of data on medical conditions and others covariates has been shown to be satisfactory.[19]

Our results are consistent with those of Canadian and Australian studies, where parity was inversely related to the risk of non-mucinous tumours, but not of mucinous ones.[2,4] Likewise, in a prospective Norwegian study,[20] the risk of serous and endometrioid tumours was inversely related to the number of births, whereas mucinous tumours showed an direct relation. Similar results also emerged in another Italian case-control study.[8] However, in three case-control studies from the USA, based on 322, 558 and 616 cases respectively[5–7] and in a pooled analysis of ten case-control studies,[21] pregnancy was associated with a reduced risk of all histologic types of ovarian cancer, in the absence of any difference for mucinous tumours.

A protective role of OC use for serous and endometrioid tumours, but not for mucinous ones, was reported in studies conducted in the USA, Canada and Sweden.[2,5,22] Further, in the WHO Collaborative Study of Neoplasia and Steroid Contraceptives,[23] the OR for ever versus never OC users for serous and endometrioid epithelial ovarian cancers was below unity, whereas that for mucinous tumours was 1.4. In a Canadian study[2] the protection of OC was apparently stronger for

Table 3 – Odds ratios (OR) of ovarian cancer and corresponding 95% confidence intervals (CI) according to histologic types and intake increase of one daily serving of selected foods groups, micronutrient and minerals (Italy, 1992–1999)

	Histologic types							
	Serous (*n* = 493)		Mucinous (*n* = 81)		Endometrioid (*n* = 78)		Other (*n* = 98)	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Meat	1.6	1.0–2.4	1.3	0.5–3.1	2.4	0.9–6.2	2.1	1.0–4.5
Fish	0.3	0.1–0.6	0.8	0.3–3.9	0.1	0.02–0.8	0.1	0.02–0.5
Vegetables	0.8	0.7–1.0	0.8	0.5–1.1	0.6	0.4–0.9	0.6	0.4–0.9
Olive oil[a]	0.8	0.7–1.0	0.9	0.6–1.3	0.6	0.4–1.0	1.0	0.7–1.4
Starch[a]	1.4	1.1–1.7	0.8	0.5–1.4	1.4	0.9–2.2	1.2	0.8–1.8
Monounsaturated fatty acid[a]	0.8	0.6–1.0	1.0	0.6–1.5	0.6	0.4–1.1	0.8	0.5–1.3
Polyunsaturated fatty acid[a]	0.8	0.7–1.0	1.2	1.0–1.6	1.1	0.8–1.5	0.8	0.5–1.1
Vitamin E[a]	0.6	0.5–0.8	1.0	0.6–1.6	0.8	0.5–1.3	0.8	0.5–1.3
β-Carotene[a]	0.9	0.8–1.0	0.9	0.6–1.3	0.8	0.6–1.3	0.7	0.5–1.1
Calcium[a]	0.9	0.9–1.1	0.8	0.5–1.2	0.4	0.3–0.7	0.8	0.5–1.1
Total (Englyst) fibre[a]	1.0	0.8–1.2	0.6	0.4–1.0	1.1	0.7–1.7	1.1	0.7–1.5

OR = Odds ratio. Multivariate estimates including terms for age, study centre, year of interview, education, parity, oral contraceptive use, family history of ovarian and/or breast cancer in first degree relatives and energy intake.
a The unit is the difference between the 80th and 20th percentile, i.e. between the upper cut-points of the fourth and first quintiles.

non-mucinous (OR = 0.89 per year of use) than for mucinous (OR = 0.98 per year of use) cancers. OC use was too limited in Italy to provide meaningful results or this issue.

With reference to HRT. Some reports have suggested that non contraceptive oestrogen use may increase the risk of endometrioid ovarian cancer, but not of other subtypes,[2,24,25] although this observation was not confirmed in other studies.[7,18,26] In our analysis no clear difference emerged between HRT use and the risk of ovarian cancer of different histologic types.

Physical activity may play a role in ovarian cancer by decreasing exposure to oestrogens, and reducing the frequency of ovulation, and consequently exposure to progesterone in the lutheal phase of the cicle.[27] Some studies found an inverse relation between various measures of physical activity and ovarian cancer,[28–30] but others found no association.[31–34] A Canadian case-control study observed a significant reduction in risk associated with higher level of moderate recreational activity for serous, endometrioid but not mucinous ovarian cancers.[35] Our data suggest a decreased risk of ovarian cancer in women with high occupational physical activity and showed no heterogeneity across histologies. Leisure time physical activity was unrelated to ovarian cancer risk. The ORs were adjusted for education and reproductive variables. Thus, the inverse association cannot be totally due to residual confounding by social class indicators. This is, however, not surprising, because of the low level and short duration of leisure time physical activity in most middle age and elderly Italian women.

Diet has also been related to ovarian cancer: several case-control studies reported a favourable effect of a diet rich in vegetables and fish on ovarian cancer risk.[36–38] Meat and fats, on the other hand, appeared to be directly related to ovarian cancer risk.[39,40] The impact of meat, fish, starch and vitamin E appeared to be less strong mucinous cancers than for other histologic types. Conversely, in a Californian case-control study, high intakes of β-carotene and vitamin E were somewhat more protective against mucinous tumours than against nonmucinous tumours, although the differences were not significant.[41] However, a recent analysis of twelve cohort studies found no significant association between vegetable intake and the risk of various histologic subtypes of ovarian cancer.[42]

In conclusion, this study provides further evidence that mucinous ovarian cancers may be in some aspect different from other types of epithelial cancer. In particular, the present study adds quantitative information indicating that the association of reproductive factors and of selected dietary habits was apparently less strong for mucinous than for other types, whereas the role of other lifestyle factors, such as physical activity, did not show significant differences across histologies.

Conflict of interest statement

None declared.

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