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Population attributable risk for ovarian cancer

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Abstract

Parity, oral contraceptive (OC) use, age at menopause, a family history of the disease and selected aspects of diet have been related to the risk of ovarian cancer. The quantification of their impact on a population level may help focus and rank the importance of potential prevention strategies. Using data from a case–control study conducted in Italy between 1983 and 1991 on 971 ovarian cancer cases and 2758 control women we computed the multivariate relative risk estimates, and population attributable risks (PARs), i.e. the proportion of ovarian cancers that would have been avoided if a given exposure had not been present in the population. Overall, the PARs were 5% for nulliparity, 12% for never OC use and 4% for a family history of breast or ovarian cancer in first-degree relatives. Among women aged $\geqslant 50$ years, later age at menopause accounted for 16% of all ovarian cancer cases. Low intake of green vegetables accounted for 24% of cases and a high fat score for 7%. All these factors together explained 51% of cases. In conclusion, even if the PAR estimates were based on several arbitrary assumptions, available knowledge could, in principle, explain over 50% of all ovarian cancer cases in this Italian population, thus indicating and quantifying the theoretical scope for prevention.

Keywords: Epidemiology; Risk factors; Women; Urinary incontinence; Frequency

1. Introduction

The aetiology of epithelial ovarian cancer is multifactorial. Parity, oral contraceptive (OC) use and early age at menopause are inversely related to the risk of ovarian cancer [1]. A family history of ovarian and breast cancer is related to the risk of the disease [2–4]. However, with the exception of ever OC use, these factors are hardly modifiable, and the public health impact of these findings is consequently minor. Among modifiable factors implied in the pathogenesis of ovarian cancer, there are also some aspects of diet. Some studies have suggested that a diet rich in saturated fats and poor in green vegetables increases the risk of the disease [1–5], although the issue remains open to debate.

The quantification of the impact of these factors on a population level may help focus and rank the importance of potential prevention strategies. In this paper, we have analysed the association between selected hormonal, familial and dietary factors and the risk of ovarian cancer, using data from a case–control study conducted in Italy [4,6]. Furthermore, we have analysed their impact on the disease on a population level, computing the population attributable risks (PAR), which are a function not only of the strength of the association, but also of the prevalence of each risk factor in the population.

2. Patients and methods

The data were derived from a case–control study on risk factors for ovarian cancer conducted in Italy between 1983 and 1991 [4,6]. Briefly, the study included 971 incident, histologically confirmed epithelial ovarian cancer cases and 2758 control women from the same catchment areas and admitted to the same hospitals as the cases, for acute, non-malignant, non-hormonal

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related conditions, who had not undergone bilateral oophorectomy. Among the controls, 34% were admitted for traumas, 30% for other orthopaedic conditions, 16% for surgical conditions and 20% for other illnesses, such as ear, nose, throat or dental disorders.

Trained interviewers used the same questionnaire to obtain information on personal characteristics and habits, a problem-oriented medical history, menstrual and reproductive factors, and history of breast or ovarian cancer in first-degree relatives. Approximately 3% cases and 4% of controls refused the interview.

Odds ratios (OR), and the corresponding confidence intervals (CI), were computed using unconditional multiple logistic regression models [7] including terms for age, calendar year at interview, area of residence, parity, OC use, age at menopause, family history of breast/ovarian cancer, green vegetable and a simplified fat score intake. PARs were computed by the method described by Bruzzi and colleagues [8], which allows them to be estimated on the basis of data from case–control studies, and are expressed as per cent in the text. The method requires the knowledge of the OR, and of the distribution of risk exposures only amongst cases, assuming that they represent the whole diseased population. Thus, using the multivariate ORs, PARs were computed for each separate factor and for various combinations of them, after allowance for confounding factors. For the sake of simplicity, the PAR for each factor was based on the assumption of moving all the subjects to the lowest level of risk of that factor. Since the logistic model assumes a multiplicative effect on the OR, the PAR for the combination of two or more factors may not be equal to the sum of the PARs for each risk factor. Variance calculations and 95% CI of the PARs (whenever computationally possible) were obtained as described by Benichou and Gail [9,10].

Table 1
Distribution of 971 epithelial ovarian cancer cases and 2758 controls according to selected variables in strata of age: Italy, 1983–1991

	All women		Women aged < 50 years		Women aged ⩾ 50 years	
	Cases $n=971$ n (%)	Controls $n=2758$ n (%)	Cases $n=352$ n (%)	Controls $n=1073$ n (%)	Cases $n=619$ n (%)	Controls $n=1685$ n (%)
Age (years)						
< 40	122 (13)	455 (16)				
40–44	78 (8)	272 (10)				
45–49	152 (16)	346 (13)				
50–54	153 (16)	393 (14)				
55–59	162 (17)	371 (13)				
60–64	150 (15)	380 (14)				
⩾65	154 (16)	541 (20)				
Menopausal status						
Post	587 (60)	1674 (61)	37 (11)	114 (11)	547 (88)	1560 (93)
Pre/Peri-	384 (40)	1084 (39)	315 (89)	959 (89)	72 (12)	125 (7)
Age at menopause (years)[a]						
< 50	256 (44)	857 (51)	37 (100)	114 (100)	219 (40)	743 (48)
50–53	252 (43)	621 (37)	– –	– –	252 (46)	621 (40)
⩾54	77 (13)	196 (12)	– –	– –	77 (14)	196 (13)
Parity[a]						
Parous	731 (76)	2162 (79)	248 (71)	803 (75)	483 (78)	1359 (81)
Nulliparous	237 (24)	590 (21)	103 (29)	269 (25)	134 (22)	321 (19)
Oral contraceptive use						
Ever	63 (6)	259 (9)	55 (16)	236 (22)	8 (1)	23 (1)
Never	908 (94)	2499 (91)	297 (84)	837 (78)	611 (99)	1662 (99)
Family history of ovarian or breast cancer in first-degree relatives[a]						
No	878 (91)	2619 (95)	323 (92)	1027 (96)	555 (90)	1592 (95)
Yes	91 (9)	138 (5)	29 (8)	46 (4)	62 (10)	92 (5)
Green vegetables (portions per week)						
⩾8	349 (36)	1307 (47)	141 (40)	507 (47)	208 (34)	800 (47)
7	355 (37)	838 (30)	119 (34)	331 (31)	236 (38)	507 (30)
⩽6	267 (27)	613 (22)	92 (26)	235 (22)	175 (28)	378 (22)
Fat score intake						
Low	490 (50)	1445 (52)	180 (51)	560 (52)	310 (50)	885 (53)
Intermediate	338 (35)	974 (35)	118 (34)	364 (34)	220 (36)	610 (36)
High	143 (15)	339 (12)	54 (15)	149 (14)	89 (14)	190 (11)

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

3. Results

Table 1 shows the distribution of ovarian cancer cases, and the comparison group according to age and selected risk factors associated in this data set with ovarian cancer risk. The corresponding ORs are shown in Table 2.

In comparison with parous women, nulliparous women were at increased risk of ovarian cancer (OR 1.3, 95% CI 1.1–1.6). Never OC users were at increased risk of the diseases (OR 1.2, 95% CI 1.0–1.7). Cases reported more frequently a later age at menopause: in comparison with women reporting menopause at age <50 years, the ORs were 1.3 (95% CI 1.1–1.6) and 1.4 (95% CI 1.0–1.9) respectively for women reporting menopause at age 50–53 years and $\geqslant 54$ years. A history of ovarian and breast cancer in first-degree relatives was associated with risk of disease (OR 1.9, 95% CI 1.9–2.5). Furthermore, cases reported a lower intake of green vegetables (OR for the lowest versus the highest tertile 1.6 95% CI 1.3–2.0) and a higher fat score intake (OR higher versus lower tertile of intake, 1.4 95% CI 1.1–1.8). The estimate ORs were consistent for the various factors in strata of women aged <50 and $\geqslant 50$ years. In particular, no significant interaction was found between age and parity or vegetable intake.

Per cent PARs for the various risk factors considered, and for selected combinations of them, are shown in Table 3. Overall, PARs were 5% for nulliparity, 12% for never oral contraceptive use and 4% for a family history of breast or ovarian cancer in first-degree relatives. Amongst women aged $\geqslant 50$ years, age at menopause accounted for 16% of all ovarian cancer cases. With regard to dietary factors, low green vegetable intake contributed to 24%, and high fat score to 7% of cases. Three factors which in principle are modifiable (dietary factors and OC use) accounted for 41% of cases, and all the six factors considered for 51% of all ovarian cases.

No marked differences emerged in the PARs estimates when the analysis was performed separately in strata of age. However, the PAR for nulliparity was lower [PAR (95% CI); 3 (0–8)], and that for low green vegetables was higher [PAR (95% CI); 30 (22–39)] in elderly women.

4. Discussion

Before discussing the results of this analysis, potential criticisms should be considered. This study has several strengths, and some of the limitations of most hospital-based case–control studies [7]. Only acute conditions, unrelated to known or potential risk factors for ovarian

Table 2
Odds ratios of ovarian cancer with 95% confidence intervals according to selected covariates: Italy, 1983–1991

	Odds ratios (95% confidence interval)[a]		
	All women	Women aged <50 years	Women aged $\geqslant 50$ years
Age at menopause (years)			
<50	1[b]		1[b]
50–53	1.3 (1.1–1.6)	–	1.3 (1.1–1.6)
$\geqslant 54$	1.4 (1.0–1.9)	–	1.4 (1.0–1.9)
Parity			
Parous	1[b]	1[b]	1[b]
Nulliparous	1.3 (1.1–1.6)	1.6 (1.2–2.2)	1.2 (0.9–1.5)
Oral contraceptive use			
Ever	1[b]	1[b]	–
Never	1.2 (1.0–1.7)	1.2 (0.9–1.8)	
Family history of ovarian or breast cancer in first-degree relatives			
No	1[b]	1[b]	1[b]
Yes	1.9 (1.4–2.5)	2.0 (1.2–3.5)	1.8 (1.2–2.5)
Green vegetables consumption (portions per week)			
$\geqslant 8$	1[b]	1[b]	1[b]
7	1.6 (1.3–1.9)	1.3 (0.9–1.7)	1.9 (1.5–2.2)
$\leqslant 6$	1.6 (1.3–2.0)	1.2 (0.8–1.6)	1.8 (1.4–2.3)
Fat intake score			
Low	1[b]	1[b]	1[b]
Intermediate	1.1 (0.9–1.3)	1.1 (0.8–1.5)	1.1 (0.9–1.3)
High	1.4 (1.1–1.8)	1.3 (0.9–1.9)	1.5 (1.1–2.0)

[a] Multivariate estimates including terms for age, calendar year at interview plus the above listed variables.
[b] Reference category.

Table 3
Per cent attributable risk (and 95% confidence intervals)[a] of ovarian cancer according to selected variables and their combination: Italy 1983–1991

	All women	< 50 years	⩾ 50 years
Late age at menopause	8[b]	–	16 (6–26)
Nulliparity	5 (1–9)	11 (3–18)	3 (0–8)
Never oral contraceptive use	12 (0–39)	14 (0–40)	–
Family history of breast and ovarian cancer	4 (2–6)	4 (1–8)	4 (2–7)
Low green vegetable intake	24 (17–31)	10 (0–25)	30 (22–39)
High fat score intake	7 (0–14)	8 (0–20)	6 (0–15)
Green vegetables + fat score intake	29	18	37
Green vegetables + fat score intake + oral contraceptive use	41	30	–
Parity + family history	10	15	6
Parity + age at menopause	13	–	15
Age at menopause + parity + family history	17	–	18
All the above factors	51	40	48

[a] When computationally possible.
[b] Giving an odds ratio of 1 to premenopausal women.

cancer, were included in the comparison group, participation was practically complete, the hospital setting should improve comparability of the information collected [11], and the questionnaire was satisfactorily reproducible and valid [12,13].

Incomplete control for confounding is conceivable, on account of the limited number of strata for categorisation of various factors, due to computational constraints for variance calculation. Any such underadjustment is, however, likely to be limited, since the ORs for most variables were not materially modified by multivariate analysis, and the PAR estimates were not appreciably changed when the number of strata of each variable was modified. Conversely, the PARs tend to be underestimated by the definition of quantiles of intake (or any other arbitrary cut-off point), which cannot identify a purely unexposed category, thus affecting the shape of the dose–risk relation.

Computation of PAR assumes that the cases are representative of all cases in the population studied, with respect to the prevalence of the risk factors investigated [8]. This is reasonable, since cases were identified in the major teaching and general hospitals of the areas under surveillance although, in the absence of a cancer registration system, the exact proportion of cases interviewed remains undefined.

This analysis shows that women with a later age at menopause, nulliparae, never OC users, and with a family history of ovarian and breast cancer in first-degree relatives are at increased risk of ovarian cancer. Furthermore, it indicates that a diet poor in green vegetables and rich in fat increases the risk of disease. Although discussion of risk factors goes beyond the scope of this paper, these data are consistent with most published findings from different populations [1,14]. The main interest of this analysis is related to the estimation of per cent population attributable risk. Overall, all factors considered accounted for 51% of all cases. In particular, this analysis under-lines, and quantifies, the potential scope for protection by oral contraceptives in a population where OC use has been, and is still, limited. We considered in the analysis a few selected dietary factors which were related to ovarian cancer risk in this as well as in other studies [1], and these factors account for 29% of all ovarian cancers in Italy. These factors should be considered essential selected indicators of a diet at high risk for ovarian cancer. A family history of ovarian and breast cancer accounted for 4% of cases in this population. With regard to potential differences in the PARs of young and old women, estimates for dietary factors were appreciably greater in older women. Translation of the present findings into preventive strategies is not without difficulties. Menstrual and reproductive factors usually cannot be changed nor can familial history of ovarian cancer. Thus, these factors cannot be used in preventive strategies. A chemoprotective use of oral contraceptive can be suggested for women at high risk of ovarian cancer [15], although a potential excess risk of breast carcinoma should be considered in women with familial breast and ovarian cancer syndromes. With regard to diet, long-term dietary modifications are possible, but not obvious, whilst specific advice is premature and awaits further evidence and quantification.

It is worth noting that to reduce the frequency of exposure to a risk factor does not always mean a reduction in the observed frequency of a disease. Thus, any translation of the present findings into preventive strategies always requires the evaluation of such strategies in clinical studies.

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