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Breast cancer risk in women with a primary ovarian cancer—a case–control study

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Abstract

Register-based studies show that women with ovarian cancer are at increased risk of developing breast cancer. Primary suggested explanations are heredity factors and a common hormonal aetiology. However, clinical surveillance that is provided for cancer patients during, and after, treatment of their primary malignancies together with possible mistakes in the registering procedures could affect the risk estimates. In order to examine these factors in women registered with ovarian cancer who develop subsequent breast cancer, a case–control study was performed. Using a regional Swedish cancer registry including 5060 women registered with ovarian cancer, 89 cases of breast cancer were found. After corrections for discrepancies in the registered and recorded information, 75 cases remained, of which 72 cases were included in the study. Information concerning possible risk factors were extracted from hospital records and compared with 177 matched controls. Suggested risk factors such as parity (relative risk (RR) = 1.41), late age at menopause (52–61 years; RR = 1.61) and heredity for breast and/or ovarian cancer (RR = 1.50) were all connected with a non-significant increased risk of subsequent breast cancer. In all, 43% of the breast cancer cases were revealed without preceding symptoms at clinical follow-up, indicating that increased clinical surveillance is a factor of importance when explaining the increased risk. The fact that only 75 (missing records included) out of the 89 registered breast cancer cases could be linked to the preceding ovarian cancer indicates that the actual risk of developing breast cancer is smaller than previously described. The clinical implications from these findings could be that, beside general screening programmes and health controls offered to women in cancer-prone families, additional mammography examinations based on the assumption of an increased risk of breast cancer are not warranted in ovarian cancer patients.

Keywords: Second primary neoplasms; Ovarian cancer; Breast cancer; Case–control study; Cancer registration; Risk factors; Survival

1. Introduction

The mechanisms of multiple malignancies appearing in the same individual are not fully understood. Suggested factors of importance are heredity [1], a common hormonal aetiology [2], and iatrogenically-induced carcinogenesis, that is chemo- and radiotherapy-induced malignancies [3–5]. An additional explanation is the impact of increased clinical surveillance and control, which commonly is provided to patients after treatment for their first primary malignancy. Furthermore, mistakes in registration procedures could also affect the finding of two or more malignancies in the same individual [6].

Women with ovarian cancer are described as having an increased incidence of second primary malignancies (SPM), according to several register-based cohort studies [7–10]. The overall risk is increased (range of standard incidence ratio (SIR) in different studies: 1.28–1.49) as well as the risk of cancers at specific sites, such as breast (SIR: 1.20–1.41), colon (SIR: 1.18–2.53), rectum (SIR: 1.43–1.73), bladder (SIR: 1.70–2.74), uterine corpus (SIR: 1.30–2.20) and leukaemia (SIR: 2.50–6.79).

The appearance of breast cancer in women with ovarian cancer fits well some of the suggested mechanisms of multiple cancer incidence, since several suggested risk factors are applicable to both cancers. For instance, parity and age at menopause are established

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risk factors of significance for both malignancies [11–15]. Furthermore, the development in cancer genetics has revealed genes strongly related to hereditary breast and ovarian cancers [16,17]. The questions to answer are if these suggested risk factors are more expressed in women with ovarian cancer and a subsequent breast cancer than in women with a solitary ovarian cancer, and if it is possible to estimate the impact of clinical surveillance and errors in registration. In order to answer these questions and to improve our knowledge of the relationships described above, a nested case–control study was designed to examine risk factors associated with a second primary breast cancer. A second aim was to compare crude survival in second primary breast cancers to crude survival after breast cancer in the general population.

2. Patients and methods

A total of 5060 patients with ovarian cancer were reported to the Stockholm-Gotland Cancer registry (a regional cancer registry in Sweden covering a population of approximately 1.8 million) during the period 1958–1992. Among them, 84 were registered with 89 diagnoses of breast cancer following the primary tumour (five were registered twice). The care of patients with gynaecological cancers in the area is centralised to the Department of Gynaecological Oncology at the Karolinska Hospital, Stockholm, which gives access to clinical data of almost all diagnosed patients. The records revealed nine errors in registration; six women had benign ovarian diseases, in two women the breast cancer was a relapse of ovarian cancer, and in one, the breast cancer was a metastasis from another SPM. Additionally, three women were excluded since their records were not retrievable, leaving 72 to be included in the study.

Three matched controls per case were chosen from the cohort of patients with ovarian cancer. Matching criteria were age at diagnosis of ovarian cancer, calendar year of ovarian cancer diagnosis, and no records of SPM in the follow-up period, which exceeded the interval between diagnosis of ovarian and breast cancer for the corresponding case (latency). In all, we were able to retrieve data on 177 controls (2.46 per case); no cases were left without controls, 37 had three controls, 31 had two controls, and 4 cases had only one control. The numbers of incomplete sets of cases and controls were mainly due to difficulties in replacing missing controls, matched to cases with long latency period.

The mean age at diagnosis of ovarian cancer among cases and controls were 58.2 and 57.4 years, respectively (Table 1). Mean latency from diagnosis of ovarian cancer to diagnosis of breast cancer was 8.0 years; for 20 cases, the latency period exceeded 10 years, 29 cases had a latency period of 4–10 years, 18 had a latency period of 1–3 years and 5 cases had less than 1 year latency period (Table 1). Corresponding cumulative frequency is displayed in Fig. 1. Stage of ovarian cancer was quite similarly distributed among cases and controls, although slightly more cases were diagnosed with stage 1 ovarian cancer (Table 1).

Detailed information on reproductive data (age at menarche, age at menopause, parity, age at first child) and heredity was extracted from the medical records together with data on histology of the ovarian cancer (World Health Organization (WHO) classification) and treatment (type of treatment, doses). Women with missing data on menopausal status (11 cases and 11 controls) were registered with menopause at 50 years of age (mean age of natural menopause in Swedish women) [18]. In 18 cases and 41 controls, menopause occurred as a result of ovarian cancer treatment (bilateral oophorectomy or radiotherapy exceeding 30 Gray

Table 1
Patient characteristics

	Cases	Controls
No. of women (2.46 controls per case)	72	177
Mean age at OC (range) (years)	58.2 (35–76)	57.4 (32–79)
Mean age at SPM (range) (years)	66.2 (37–86)	–
Mean latency to SPM (range) (years)	8.0 (0–29)	–
<1 year	5	–
1–3 years	18	–
4–10 years	29	–
>10 years	20	–
Stages of ovarian cancer		
Stage 1	44 (61%)	96 (54%)
Stage 2	11 (15)	27 (15)
Stage 3	8 (11)	29 (16)
Stage 4	2 (3)	5 (3)
Stage not registered	7 (10)	20 (11)

OC, ovarian cancer; SPM, second primary malignancies; stages according to International Federation of Gynecology and Obstetrics (FIGO).

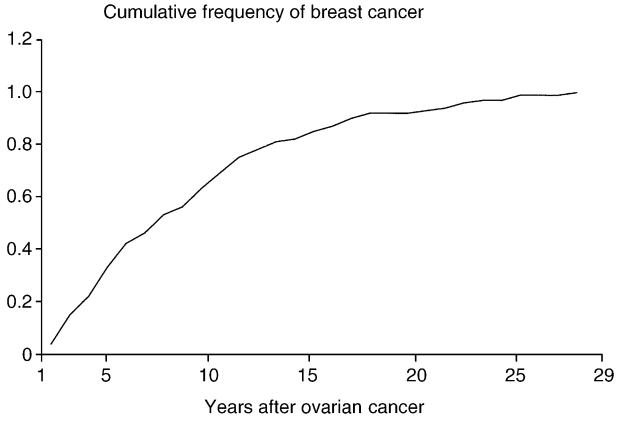

Fig. 1. Cumulative frequency of breast cancer in 72 women with ovarian cancer and subsequent breast cancer.

to the pelvis). They were excluded from the analysis concerning age at menopause and the risk of developing breast cancer. Information concerning hormonal treatment was quite sparse in the records and not used in the evaluation.

Data concerning family history of cancer was limited to first-degree relatives, primarily registering ovarian and/or breast cancer, but information on cancer incidence, in general, was also collected. Validity of the information concerning heredity was considered high regarding the appearance of cancer among first-degree relatives, although detailed information on site and diagnosis were often less specific, according to a previous in-department quality control (data not shown).

The relative risk (RR) of developing breast cancer in relation to investigated risk factors was calculated by using conditional logistic regression analysis by the model for case–control studies using matched controls, suggested by Breslow and Day [19]. Calculations of statistical power, by methods suggested by Schlesselman [20], revealed that a relative risk of 2.2 could be established with 80% power, assuming a 50% exposure, while a relative risk of 1.5, assuming the same exposure, could be established with 30% power. To estimate the impact of increased clinical surveillance, information was collected on how and where the breast cancer was diagnosed, together with information on possible symptoms preceding the breast cancer. Data were missing for 13 cases concerning the mode of detection and for an additional 3 cases information was missing regarding the appearance of symptoms. Crude survival after breast cancer diagnosis was calculated by actuarial life-table method according to Cutler-Ederer described by Dawson-Saunders and Trapp [21] and compared with nation-based crude survival data in breast cancer patients [22]. Patients with relapsing ovarian cancer were excluded from the analysis on breast cancer survival.

3. Results

The risk of developing breast cancer was increased, but not statistically significant, for women with heredity for breast and/or ovarian cancer (RR = 1.50; 95% confidence interval (CI): CI: 0.52–4.28) (Table 2). Heredity in general, i.e. the occurrence of any malignant disease among first-degree relatives, resulted in an almost 2-fold significant increased risk (RR = 1.94; 95% CI: 1.01–3.72).

Reproductive factors such as nulliparity (RR = 1.41), late age at menopause (RR = 1.70) and high late at first childbirth (RR = 1.43) were associated with an increased risk of breast cancer, however without statistical significance. Women reporting menarche before the age of 14 years had a non-significant decreased risk (RR = 0.60; 95% CI: 0.29–1.28).

Cases and controls with ovarian cancer of borderline malignancy were used as reference when estimating the risk of breast cancer in relation to the histological type of ovarian cancer. Women with mucinous ovarian cancer revealed a significantly increased risk (RR = 3.80; 95% CI: 1.23–11.78). With the exception of endometroid tumours, the other histological types of ovarian cancer was observed with a non-significant increased risk.

Potentially carcinogenic treatment with radio- or chemotherapy did not increase the risk of developing breast cancer, either used alone or together.

When investigating the mode of detection, 56 records with accurate information concerning breast cancer

Table 2
Risk of breast cancer with established and suggested risk factors[a]

	Cases *n* (%)	Controls *n* (%)	RR (95% CI)
Heredity of breast and/or ovarian cancer			
Negative	57 (90%)	152 (94%)	–
Positive	6 (10)	9 (6)	1.50 (0.52–4.28)
General heredity			
Negative	40 (63)	121 (75)	–
Positive	23 (37)	40 (25)	1.94 (1.01–3.72)
Age at menopause (years)			
40–48	15 (28)	44 (23)	–
49–51	18 (33)	55 (41)	1.10 (0.47–2.57)
52–61	20 (37)	37 (27)	1.70 (0.76–3.81)
Parity			
1+	42 (59)	119 (68)	–
0	29 (41)	57 (32)	1.41 (0.78-2.56)
Age at 1st partus (years)			
⩽29	23 (70)	81 (76)	–
⩾30	10 (30)	26 (24)	1.43 (0.52–3.91)
Age at menarche (years)			
⩾14	31 (61)	67 (54)	–
⩽13	20 (39)	57 (46)	0.60 (0.29–1.28)
Histological class			
Borderline	6 (8)	26 (15)	–
All ovarian cancers	66 (92)	151 (85)	2.05 (0.94–5.36)
1 (serous)	26 (36)	61 (34)	1.97 (0.72–5.41)
2 (mucinous)	17 (24)	22 (12)	3.80 (1.23–11.78)
3 (endometroid)	7 (10)	29 (16)	1.00 (0.27–3.73)
Other epithelial	7 (10)	19 (11)	1.67 (0.45–6.15)
Granulosa cell	9 (13)	20 (11)	2.49 (0.68–9.18)
Chemotherapy			
Negative	38 (53)	87 (49)	–
Positive	34 (47)	90 (51)	0.76 (0.39–1.46)
Radiotherapy			
Negative	26 (36)	51 (29)	–
Positive	46 (64)	126 (71)	0.70 (0.39–1.25)

RR, relative risk. Statistical significance with 95% confidence interval (95% CI). –, reference in each comparison.

[a] Due to missing or excluded data, numbers add up to less than the totals of 72 and 177 in some categories.

Table 3
Mode of detection and appearance of symptoms in association with the diagnosis of second primary breast cancer

Mode of detection	Symptoms	
	Yes	No
Oncological controls	14	17
Other regular controls	2	1
Non-regular control[a]	15	0
Public screening	0	4
Simultaneous diagnosis	1	2
Total[b]	32	24

[a] Extra examinations due to symptoms.
[b] Information was missing in 16 cases.

detection were available. In all, 24 tumours (43%) were found without records of preceding symptoms, out of which 17 (30%) were revealed during routine oncological follow-up, one (2%) at other regular medical controls, four (7%) through public screening by mammography and two (4%) simultaneously with the ovarian cancer (Table 3). The remaining 32 cases of breast cancer (57%) were detected in connection with some kind of symptoms, urging the patient to seek a physician or mention the symptom at their regular control (Table 3).

Crude survival after second primary breast cancer was found not to differ from nation-based crude survival after breast cancer (Fig. 2).

4. Discussion

Breast and ovarian cancer share several factors of common aetiology, which possibly could explain the increased risk of subsequent malignant breast tumours described after ovarian cancer. The two cancers are to some extent hormone-dependent and female reproductive factors such as nulliparity, early menarche, late menopause and late age at first childbirth are considered risk factors of major or minor significance for the two malignancies [11–15]. Hormonal replacement therapy (HRT) given to an increasing number of peri- and postmenopausal women has been proven to increase the risk of breast cancer [23,24], while the risk of ovarian cancer related to HRT is more uncertain [11]. Further evidence of oestrogen exposure as a risk factor for breast cancer is the previous established relationship between granulosa-cell tumours—normally oestrogen-producing — and subsequent breast cancer [25]. Histological type of ovarian cancer has not previously been convincingly connected with the risk of breast cancer, although there are suggested links between serous ovarian adenocarcinomas and SPM of the breast [9,26]. Evidence of an aetiological connection is further strengthened by the findings that ovarian cancer incidence is similarly increased in breast cancer patients, although there are conflicting data concerning this relationship [27–29].

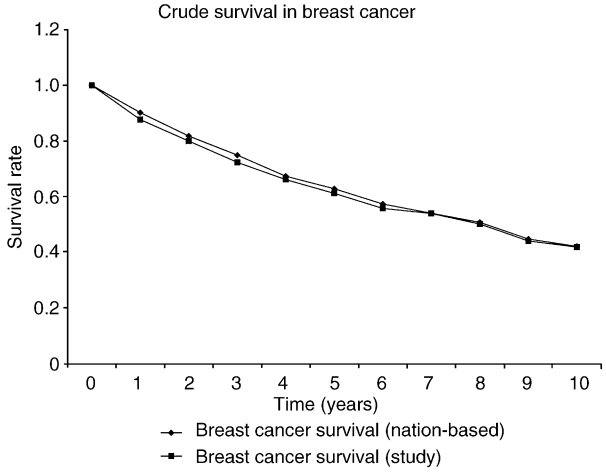

Fig. 2. Crude survival 0–10 years after breast cancer diagnosis. Nation-based survival compared with survival after second primary breast cancer in 72 women with ovarian cancer and subsequent breast cancer. Deaths in ovarian cancer are excluded.

According to the findings in this study, reproductive risk factors, i.e. parity, age at first childbirth and age at menopause, are more expressed in women with multiple malignancies of the ovary and breast, although the findings lack statistical significance. The decreased risk of breast cancer connected to a low age at menarche found in the present study is opposite result compared with previous data, but the lack of statistical power and the great number of data supporting the opposite connection makes it unlikely that this finding needs further consideration. Women with mucinous ovarian cancer were at a higher risk of developing breast cancer, as well as women with serous adenocarcinomas and granulosa cell tumours, although the connections lacked statistical power. The latter findings have previously been linked to an increased incidence of breast cancer [9,25,26]. Mucinous ovarian cancer, however, has not previously been suggested as a risk factor for breast cancer and this finding needs future investigation.

Contrary to leukaemia [4], breast cancer does not seem to be induced by chemotherapy, and despite the fact that, with the exception of the bone marrow and the childhood thyroid gland, the premenopausal female breast, is the most radiosensitive tissue of the body [3], breast cancer risk was not found to be related to radiotherapy treatment. This could probably be explained by the low breast doses absorbed in conventional ovarian cancer treatments.

Developments in the field of cancer genetics, which in the mid-1990s revealed common high penetrance genes for hereditary breast and ovarian cancer, *BRCA-1* and *BRCA-2*, gives additional understanding to multiple malignancies of the breast and ovary [16,17]. Hereditary

factors are suggested to constitute 5–10% of all ovarian and breast cancers, but germ-line mutations in *BRCA-1* or *BRCA-2* are only identified in 2–3% of all breast cancer cases. Thus, investigators have suggested the existence of additional genes that influence the risk of developing cancer [30]. In our study, the appearance of other malignant diseases among close relatives were associated with an increased risk. This could be interpreted as a sign of a more general susceptibility to cancer in these families, possible influenced by as yet unknown hereditary traits.

The impact of increased clinical surveillance in explaining the increased risk of SPM has been difficult to measure. Theoretically, thorough examinations by physicians at regular intervals would make it possible to bring forward the diagnosis of indolent tumours or tumours with a low malignancy potential, which otherwise would have been detected much later, or never would have been diagnosed. For breast cancer in ovarian cancer patients, this would certainly be applicable if the regular control includes breast examination and mammography. This theory is also in agreement with the noticed decrease in risk over time after ovarian cancer diagnosis [9,10]. The present study revealed that numerous breast cancers were detected by manual and/or mammography examinations in women with no symptoms of the disease, that is, at routine follow-up at the department of gynaecological oncology. The result definitely suggests that clinical surveillance should be an issue in future epidemiological studies dealing with SPM and, furthermore although the validity of the recorded information might be disputable, indicates that clinical surveillance is a factor of importance when trying to explain the increased risk of breast cancer.

Mistakes in registration procedures could also affect the risk estimates of SPM. A previous study based on the same cancer registry revealed that the risk of breast cancer was smaller than previously calculated after correction for mistakes in registration [6]. Corrections for double registrations were not used in that study, implying the actual risk to be even smaller. Errors in registration further question whether register data is optimal when assessing the risk of second primary neoplasms. Instead, case–control studies might be preferable.

Crude survival in SPM of the breast seems similar to crude survival in primary breast cancer. This could be interpreted as the malignancy potential of the first primary and second primary breast cancers being comparable, but interpretations of these findings should be made with caution, since data is sparse and crude survival analysis is far from the most optimal technique to use.

However, the results of this study indicate that a substantial part of the previously described increase in breast cancer incidence among women with ovarian cancer could be based on errors in registration and an effect of increased clinical surveillance. These findings could be used in discussions concerning HRT in women treated for ovarian cancer. Suspicions of a higher risk of breast cancer have in some countries excluded this group of women from HRT, whereas in other countries, HRT use is more widely accepted. The results of this study, indicating a low risk, could be used to promote the concept of liberal use of HRT. However, little is known about the risk of adverse effects of HRT use in cancer patients generally, and the results of this study lack the statistical power to be conclusive in this matter.

With reservations due to the lack of statistical significance, further clinical implications from the findings of this study could be that beside general screening programmes and health controls offered to women in cancer-prone families, additional mammography examinations based on assumptions of an increased risk of breast cancer are not warranted in ovarian cancer patients. This conclusion is further strengthened by the widespread latency time from ovarian cancer to subsequent breast cancer, implying the absence of any special time period connected with an increased risk where screening efforts might be fruitful.

References

1. Lynch HT, Fusaro RM, Lynch J. Hereditary cancer in adults. *Cancer Detect Prev* 1995, **19**, 219–233.
2. Henderson BE, Feigelson HS. Hormonal carcinogenesis. *Carcinogenesis* 2000, **21**, 427–433.
3. United Nations Scientific Committee on the Effects of Atomic Radiation. *Sources and Effects of Ionizing Radiation. UNSCEAR 1994 Report to the General Assembly, with Scientific Annexes*. New York, United Nations, 1994.
4. Travis LB, Holowaty EJ, Bergfeldt K, *et al*. Risk of leukemia after platinum-based chemotherapy for ovarian cancer. *N Engl J Med* 1999, **340**, 351–357.
5. Day NE, Boice JD Jr. Summary chapter. In Day NE, Boice JD, eds. *Second Cancer in Relation to Radiation Treatment for Cervical Cancer. IARC Scientific Publications No. 52*. Lyon, France, International Agency for Research on Cancer, 1983, 137–184.
6. Bergfeldt K, Silfversward C, Einhorn S, Hall P. Overestimated risk of second primary malignancies in ovarian cancer patients. *Eur J Cancer* 2000, **36**, 100–105.
7. Sankila R, Pukkala E, Teppo L. Risk of subsequent malignant neoplasms among 470 000 cancer patients in Finland, 1953–1991. *Int J Cancer* 1995, **60**, 464–470.
8. Storm HH, Ewertz M. Second cancers following cancer of the female genital system in Denmark, 1943–1980. *Natl Cancer Inst Monogr* 1985, **68**, 331–340.
9. Travis LB, Curtis RE, Boice JD Jr. Second malignant neoplasms among long-term survivors of ovarian cancer. *Cancer Res* 1996, **56**, 1564–1570.
10. Bergfeldt K, Einhorn S, Rosendahl I, Hall P. Increased risk of second primary malignancies in patients with gynecological cancer. A Swedish record-linkage study. *Acta Oncol* 1995, **34**, 771–777.
11. Riman T, Persson I, Nilsson S. Hormonal aspects of epithelial ovarian cancer: review of epidemiological evidence. *Clin Endocrinol (Oxf)* 1998, **49**, 695–707.

12. Hankinson SE, Colditz GA, Hunter DJ, *et al*. A prospective study of reproductive Factors and risk of epithelial ovarian cancer. *Cancer* 1995, **76**, 284–290.
13. Adami HO, Hsieh C, Lambe M, *et al*. Parity, age at first childbirth, and risk of ovarian cancer. *Lancet* 1994, **344**, 1250–1254.
14. Lambe M, Hsieh C, Chan H, Ekbom A, Trichopoulus D, Adami HO. Parity, age at first and last birth, and risk of breast cancer. A population based study in Sweden. *Breast Cancer Res* 1996, **38**, 305–311.
15. Lipworth L. Epidemiology of breast cancer. *Eur J Canc Prev* 1995, **4**, 7–30.
16. Skolnick MH, Frank T, Shattuch-Eidens D, Tavtigian S. Genetic susceptibility to breast and ovarian cancer. *Pathol Biol (Paris)* 1997, **45**, 245–249.
17. Ford D, Easton DF. The genetics of breast and ovarian cancer. *Br J Cancer* 1995, **72**, 805–812.
18. Anon. Statement of consense on prevention with estrogens after menopause. *Lakartidningen* 1996, **93**, 4557–4561 (in Swedish).
19. Breslow NE, Day NE. Conditional logistic regression for matched sets. In *Statistical Methods in Cancer Research, Volume 1—The Analysis of Case-Control studies*. *IARC Scientific Publications No. 32*. Lyon, France, International Agency for Research on Cancer, 1980, 248–279.
20. Schlesselman JJ. Sample size requirements in cohort and case–control studies of disease. *Am J Epidemiol* 1974, **99**, 381–384.
21. Dawson-Saunders B, Trapp RG. Methods for analyzing survival data. In *Basic & Clinical Biostatistics*. NJ, Prentice Hall International, 1994, 188–209.
22. Stenbeck M, Rosén M, eds. Cancer survival in Sweden 1961–1991. *Acta Onc* 1995, **34**(Suppl. 4.).
23. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* 2000, **283**, 485–491.
24. Magnusson C, Baron JA, Correia N, Bergström R, Adami HO, Persson I. Breast-cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy. *Int J Cancer* 1999, **81**, 339–344.
25. Björkholm E, Sifversward C. Incidence and occurence of second primary tumours after granulosa cell tumours. *Acta Radiol Oncol* 1980, **19**, 161–167.
26. Shah S, Evans DGR, Blair V, Burnell LD, Birch JM. Assessment of relative risk of second primary tumors after ovarian cancer and the usefulness of double primary cases as a source of material for genetic studies with a cancer registry. *Cancer* 1993, **72**, 819–827.
27. Brenner H, Siegle S, Stegmaier C, Ziegler H. Second primary neoplasms following breast cancer in Saarland, Germany, 1968–1987. *Eur J Cancer* 1993, **29**, 1410–1414.
28. Ewertz M, Storm HH. Multiple primary cancer of the breast, endometrium and ovary. *Eur J Cancer Clin Oncol* 1989, **25**, 1927–1932.
29. Adami H-O, Bergkvist L, Krusemo U-B, Persson I. Breast cancer as a risk factor for other primary malignant diseases. *JNCI* 1984, **73**, 1049–1055.
30. Rubin SC, Blackwood MA, Bandera C, *et al*. BRCA1, BRCA2, and hereditary nonpolyposis colorectal cancer gene mutations in an unselected ovarian cancer: relationship to family history and implications for genetic testing. *Am J Obstet Gynecol* 1998, **178**, 670–677.