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Special Paper

Early Detection of Familial Ovarian Cancer

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When ovarian cancer is detected at an early stage, prognosis is good, which has led to discussion of a screening programme. The aim of this study was to identify and examine women at high risk of familial ovarian cancer, and to evaluate the inclusion criteria and the diagnostic methods for early detection of ovarian cancer. We report the first round screening findings in a prospective study of 180 women (mean age 43.4 years) considered to be at high risk of ovarian cancer based on family history. They were subjected to gynaecological examination with transvaginal ultrasound (TVU), CA125 and breast examination. Of these, 13 women with oestrogen receptor positive breast cancer had therapeutic oophorectomy and the ovaries were histologically examined. Among 180 women examined, nine ovarian cancers (among them two found at oophorectomy because of breast cancer) (mean age 49.0 years), seven benign tumours of the ovary (mean age 48.1 years), one cancer of the cervix, and four breast cancers were diagnosed. The prevalence of ovarian cancers (5%) was significantly more than in any previous series. TVU as a diagnostic method proved useful and detected 7/9 cancers, whereas CA125 was elevated in 4/9 cancers. To our knowledge, this is the first programme which has successfully delineated a high risk group and prospectively demonstrated their high prevalence of ovarian cancer. Possible biases are discussed.

Key words: familial ovarian cancer, familial breast cancer, screening, transvaginal ultrasonography
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INTRODUCTION

OVARIAN CANCER is the leading cause of a gynaecological cancer death in young adult women in the Western world. Over the past 15 years, the incidence has either been stable or steadily increasing in most industrialised countries [1]. In Norway, the yearly incidence of ovarian cancer is 461 (19.8/100000 women/years), and represents 6% of the total number of all new cancer cases in women from 1986 to 1990 [2]. Although the aetiology of ovarian cancer is poorly understood, both genetic and epidemiological factors have been described. A family history of ovarian cancer is the strongest risk factor. Associations related to ovulation pattern, nulliparity and high age at first childbirth have also been reported [3].

Hereditary ovarian cancer is heterogeneous and may account for more than 5% of ovarian cancers [1]. One gene, referred to as *BRCA1*, located on chromosome 17q21 [4, 5] predisposes women to breast and ovarian cancer. This gene may account for the inherited predisposition to cancer in 80% of the families with multiple breast and ovarian cancers, and about 45% of all early onset breast cancer in families without ovarian cancer [5, 6]. There is no verified risk to male carriers. For female gene carriers, the cumulative risk is 44% for ovarian cancer and 87% for breast cancer by the age of 70 years [7]. Mutation tests for *BRCA1* to identify gene carriers were not available at the time of the study, and linkage analyses can only be done in a few large, informative families.

Early stages of ovarian cancer display no specific symptoms or signs. The prognosis is good when the disease is diagnosed early (stage I–II) with 80–95% 5-year survival. However, by the time the patients seeks medical help, the majority (about 60–70%) already have widespread intra-abdominal disease (FIGO stage III–IV), with an expected 5-year survival of less than 25% [8].

To our knowledge, neither general screening programmes for ovarian cancer [8–11], nor programmes for women with increased risk of ovarian cancer, have been successful, but some have, in retrospect, made estimations from the results and concluded that it would have been cost-beneficial to screen certain subgroups [11–17]. Published studies which used a family history of ovarian cancer as an inclusion criteria have shown diversity in selection criteria (Table 1). Our

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Table 1. Reports on previous studies with transvaginal ultrasound and CA125 in women at risk of familial ovarian cancer, compared with present study

[Ref.]	No. oc found/ No. examined	(Prevalence)* P†	Mean age oc/examined	Inclusion criteria
Granberg *et al.* 1988 [12]	0/115	(0.0) 0.019	— /45.6	One 1st degree, 2nd degree or 3rd degree relative with oc
Karlan *et al.* 1993 [17]	1/597	(1.6) 0.000	— / —	One 1st degree relative with either colon, breast, endometrial or oc or one 2nd degree relative with oc
Muto *et al.* 1993 [15]	0/386	(0.0) 0.000	— /41	One 1st degree or multiple 2nd degree relatives with oc
Bourne *et al.* 1993 [14]	6/1601	(3.7) 0.000	46.2/47	One 1st degree or 2nd degree relative with oc
Present study	9/180	(50)	49/43.4	See Table 2

oc, ovarian cancer. *Per thousand. †Fisher's exact *P* compared with present study.

clinical criteria for defining women at risk for breast and/or ovarian cancer is given (Table 2), and have been published previously [18]. They include recent knowledge that most inherited ovarian cancers are seen in the combined breast/ovarian cancer families, and are supposed to be more specific than criteria used by others [12, 14, 15, 17].

The aims of our study were to identify women at risk of ovarian cancer and to evaluate the examination protocol for early detection of ovarian cancer. We report the results of the first annual screening in 180 women considered to be at risk.

PATIENTS AND METHODS

Between January 1992 and November 1994, a prospective study was performed, recruiting asymptomatic (previous breast cancer accepted) women with a history of ovarian and breast cancer in the family. They were referred by their local hospital or doctor or self-referred for genetic counselling at our hospital. Our selection criteria are shown in Table 2. Women were considered to be at risk if they were first degree relatives of a diseased woman in the affected families, or were second degree relative to an affected woman through male, as described in Table 2. Extended pedigrees with first and second degree relatives, including affected and non-affected, were obtained. When cancer was reported, the histopathological diagnoses of relevant relatives necessary for the inclusion criteria were histologically confirmed. Initially, each woman received genetic counselling either alone or together with her family.

Eligible for the study were 180 women (mean age 43.4 years). Examination started from 25 years of age or whenever the patients were included ($n=170$). In families with onset of cancer before 30 years of age, examination started 5 years earlier than the youngest affected ($n=10$, age at examination ranged from 18–24 years).

Table 2. Clinical criteria for hereditary breast/ovarian cancer. Women at risk are first degree relatives (sisters or daughters) or second degree relatives through male of one of the following diseased women

1. One with ovarian cancer who has one first degree relative, or second degree relative through male with ovarian cancer or breast cancer (breast cancer diagnosed ≤ 60 years).
2. One diseased with both ovarian and breast cancer (breast cancer diagnosed ≤ 60 years).

The physical examination included breasts, gynaecological examination and measurement of serum CA125. The breast examination included palpation and mammography, supplemented with ultrasound and aspiration cytology whenever necessary. The gynaecological examination included a cervical smear and transvaginal ultrasound (TVU) (B & K 3535) with a mechanical vaginal probe (7.5 MHz) of the ovaries and uterus. Multicystic cysts (more than two), thick septa, excrescences, irregular patterns and variety of the sonolucency of the tumours were notified as possible malignant features [8, 10, 19]. All women with tumours of the ovaries, observed with TVU, received surgery. Simple uni- or bilocular thin walled cysts of the ovaries were not considered as tumours. If the diameter was more than 2 cm, the examination was repeated 2–3 months later. If they persisted or increased in size, laparoscopy was performed with resection or extirpation of the ovary. Women with previous oestrogen receptor positive breast cancer were, after the examination, considered for oophorectomy as part of their treatment.

The serum tumour marker CA125 was determined, the reference limit being 35 U/ml [20]. If elevated, a new sample was taken 2–3 months later, and when persistent, laparoscopy was performed.

All histological slides of the cancers were reviewed in the Department of Pathology at our hospital. Histological classification was based on the criteria defined by the WHO [21]. Clinical staging was according to the systems adopted by the International Federation of Gynecology and Obstetrics (FIGO) [1].

Statistical analysis

The prevalence of ovarian cancer in our study was compared with previous reports by Fisher's exact *P* (one-sided). Sensitivity, specificity, and positive and negative predictive values were calculated for TVU and CA125 selectively, considering the combined findings as the 'true' values (Tables 3, 4 and 5).

RESULTS

Pelvic surgery was performed in 27 patients. Abnormal TVU lead to surgery in 14 patients, 7 had cancer and 7 had benign neoplasms. 13 patients with normal TVU had oophoretomy on the basis of previous breast cancer, two of

Table 3. Histopathology of the ovarian cancers, stage, DNA-ploidy, grade, CA125, ultrasound findings, age of ovarian cancer, age of first and second breast cancer

Case	Histologic type	Stage	Ploidy	Grade	CA125 (U/ml)	Ultrasound findings	Age oc	Age breast cancer 1st/2nd
1	Granulosa cell-tumour	I	NE‡	—	11	Difficult to interpret	51	50
2	Borderline mucinous cystadenoma	I	dip§	—	16	Unilocular cyst thick wall	54	42/51
3	Borderline serous papillary cystadenoma	I	dip§	—	16	Multicystic, solid component	44	—
4	Borderline serous papillary cystadenoma	I	dip§	—	74	Multicystic, papillary formations	53	46
5	Adenocarcinoma†	II	dip§	3	32	One enlarged ovary	48	36/40
6	Adenocarcinoma†	III	NE‡	3	197	Multicystic, solid parts	35	—
7	Serous papillary adenocarcinoma	III	NE‡	3	21	Multicystic, solid parts	65	—
8	Mixed serous and endometrioid adenocarcinoma	III	NE‡	3	1364	Multicystic, thick septa, solid parts	50	37
9	Serous cystadenocarcinoma	III	NE‡	3	1416	Multicystic thick septa, solid parts	41	—

Mean age oc: 49 years. Mean age breast cancer 1st/2nd: 42.2/45.5 years.
oc, ovarian cancer. †Not specified. ‡NE, not evaluated; §dip, diploid.

Table 4. Histopathology of the benign and/or the potential premalignant ovarian tumours, age at diagnoses, CA125 and ultrasound findings

Case	Age (years)	Histology	CA125 (U/ml)	Ultrasound findings
B1	73	Serous, papillary cystadenoma	10	Multicystic, considered benign
B2	26	Serous, papillary cystadenofibroma	12	Unilocular cyst
B3	35	Serous cystadenofibroma	57	Unilocular cyst
B4	49	Serous cystandenofibroma	22	Unilocular cyst, papillary formation
B5	62	Serous cystadenoma	10	Unilocular cyst
B6	53	Mucinous cystadenoma	17	Unilocular cyst
B7	39	Endometrioma	35	Heterogenic, sand grain-like, tumour

Table 5. Ultrasound findings and the surgical evaluation of these findings in women examined

	Transvaginal ultrasound		
	Normal	Abnormal	Total
No surgery	153	0	153
Surgical evaluation			
Normal ovaries	11*	0	11
Benign neoplasm	0	7†	7
Malignant neoplasm	2*	7‡	9
	166	14	180

*Oophorectomy on the basis of previous breast cancer. †Six benign-looking tumours and one suspected malignant at transvaginal ultrasound (TVU). ‡All suspected malignant at TVU.

whom proved to have ovarian cancer (details are given below and in Table 5). Thus, 16/180 (8.9%) patients had abnormal ovarian findings after pelvic surgery, simple cysts not included. Of these, 9 (95% confidence interval 4.1–17.1; 5%) women had ovarian cancer and 7 (3.9%) had benign tumours of the ovaries. In addition, 4 women had breast cancer (mean age 40 years, range 38–43 years). Details of these breast cancer patients form part of another prospective study reported separately [22]. One woman had cancer of the cervix.

The characteristics of the ovarian cancers are listed in Table 3. There were three borderline tumours (FIGO stage I), five adenocarcinomas (one stage II and four stage III), and one granulosa cell tumour (stage I). The mean age was 49 years (range 35–65 years). Relevant parts of the pedigrees for these women are shown in the Appendix.

13 women with breast cancer, including the 4 diagnosed in this examination, were treated with oophorectomy. Among the women who were diagnosed with ovarian cancer, 5 already

had breast cancer (2 had bilateral breast cancer), mean age at time of first breast cancer was 42.2 years (Table 3). 2 of them (cases 1 and 5) had therapeutic oophorectomy and histopathological examination of the ovaries demonstrated cancer (stage I and stage II). Both patients had no macroscopic evidence of cancer at surgery, peritoneal washing showed no malignant cells. Pre-operative TVU findings are listed in Table 3. In case 1, TVU of the right ovary was described: "not well visualised, no malignant signs". Four weeks later she had her ovaries removed, the pathological report described a $1.2 \times 1.4 \times 1.7$ cm tumour of the right ovary, homogeneous in appearance. In case 5, the right ovary was enlarged at TVU and 3 weeks later at surgery it measured $3.5 \times 3.5 \times 3$ cm (compared to the left ovary: $2.6 \times 1 \times 0.7$ cm). The ovarian stroma was replaced by a compact tumour without cysts.

The histologies of the benign tumours are listed in Table 4. The mean age was 48.1 years (range 26–73 years). All the benign ovarian tumours were diagnosed with TVU, case B4 had malignant features (Table 4).

All TVU findings of ovarian tumours ($n=14$) were confirmed at surgery (Table 5). Seven out of nine malignancies had malignant features at TVU. The largest diameters of the malignant tumours in stage I and II, cases 2, 3 and 4, measured 5.5, 5 and 7 cm, respectively. Two malignancies were considered benign at TVU, case 5 showed one enlarged ovary and case 1 was difficult to interpret (Table 3). From these figures, we derived, within the limitations of the study design, that for the diagnosis of ovarian cancer the TVU findings of suspected malignancy had a sensitivity of 78% (7/9), a specificity of 99.4% (170/171), a positive predictive value 87.5% (7/8) and a negative predictive value of 98.8% (170/172).

Within the first year after the examination, 100 of the women had not developed interval cancer, the rest had their first examination more than 6 months ago without having developed symptoms of cancer yet. We continue with annual screening.

Serum CA125 was elevated in four out of nine ovarian cancer cases (3 stage III and one stage I) (Table 3), and in one out of the seven benign ovarian tumours (Table 4). Among the rest of the examined women, 4 had elevated values (35–80 kU/l), and 2 had laparoscopy performed for that reason. One woman with normal TVU had endometriosis, the other had a simple ovarian cyst at TVU and at laparoscopy. From these figures, we derived, within the limitations of the study design, that the sensitivity of an elevated CA125 for diagnosing ovarian cancer was 44% (4/9) and the specificity 97% (166/171). Positive predictive value was 44% (4/9) and negative predictive value was 97% (166/171). None of the ovarian cancers were diagnosed by CA125 alone.

As seen in Table 1, we found significantly more ovarian cancers than in previous studies listed.

DISCUSSION

Seven ovarian cancers (3.9%) and four breast cancers, a total of 11 cancers (6.1%) out of 180 women in the first round screening, together with the two ovarian cancers found following protocol treatment of previous breast cancer (a total of 13/180, 7%) verifies that our selection criteria and protocol were successful in delineating a true high risk group. This verifies that ovarian cancer continues to occur in these families. The young age at onset may also indicate that their cancers are inherited. Mean age was 49 years (Table 3) (median age 50 years) which is comparable with other studies [23], in contrast to median age of 65 years in sporadic ovarian cancer in Scandinavia [2].

The ultrasound technique has been considerably improved with the introduction of the transvaginal probe. Morphological characteristics of the ovaries have been found to be quite reproducible, and different sets of criteria for malignancy have demonstrated high sensitivity [8, 19]. All but two of the cancers (cases 4 and 9) were suspected malignant at TVU. However, 4 of these cases were grade III and were diagnosed by palpation as well. Of the early cases, 3 out of 5 were borderline cancer with good prognoses, but it remains to be verified whether TVU can detect cancer before spread and thereby improve the survival.

All the benign ovarian tumours were diagnosed by TVU, and one had a malignant feature. We do not consider a false positive result to be a problem in this high risk group, as this would only lead to laparoscopy or at worst unilateral oophorectomy in a high risk person. Overall, TVU proved to be an important diagnostic tool.

The tumour marker serum CA125 is usually not recommended for screening because of non-specified increases detected in several inflammatory diseases, pregnancy and endometriosis [20]. CA125 has been reported to be elevated in only 23–50% of stage I ovarian cancer patients [24]. Again, low specificity would be acceptable, while low sensitivity would make the test of limited value. CA125 in serum was only elevated in 4 out of 9 women with ovarian cancer (Table 3). 3 of these patients had advanced disease and the tumours were diagnosed both clinically and by TVU. Of the 5 patients with early diagnosed cancers with good prognoses (stage I and II), only one had slightly elevated CA125 (case 4), but she also had abnormal TVU findings. In this series of high risk women examined, CA125 did not identify any diseased patients not also demonstrated by TVU (Tables 3 and 4), and the sensitivity was low. In accordance with previous studies, we conclude that CA125 is not effective for diagnosing early cancer [24].

Recent reports on morphological changes in "normal ovaries" removed on prophylactic indications in patients with a strong family history, reveal a high prevalence of abnormalities as irregular surface characteristics, epithelial hyperplasia, stromal hyperthecosis, and microcystic "cystadenomas" [25]. We also found benign tumours, seven out of 180 (3.9%) (Table 4). Two were serous, papillary cystadenomas which may be difficult to distinguish from borderline tumours. The cystadenomas might also have a malignant potential. However, our figures are small, and hopefully future studies will gain more knowledge of the premalignant lesion and the carcinogenic process, necessary for interpretation of these findings. Screening strategies aimed at either cancer prevention (such as conventional drugs, gene therapy, etc.) or early detection, and whether familial ovarian cancer differs from the sporadic one, will be dependent upon such knowledge. An accurate family history will always be useful for risk estimation and planning of medical surveillance for genetic cancers. The *BRCA1* gene is complex [26], and should be better described before routine testing can be considered for clinical use. Only some mutations seem to carry a risk for ovarian cancer [7]. If a control regimen cannot guarantee safety for women at risk of ovarian cancer, future genetic testing providing high risk estimates may increase demand for prophylatic oophorectomy.

The high prevalence of ovarian cancer demonstrated, may

prompt concern over biases. One factor is the small number examined. Another factor may be self-referral of symptomatic women claiming to be asymptomatic. This was checked for in the genetic counselling prior to examination. Lack of random sampling is a problem, but according to Norwegian law it is illegal to approach family members who are not referred or self-referred for genetic counselling. The follow-up and expansion of the study will clarify this. However, it may be that genetic cancer has long-standing asymptomatic precancers or cancers which were detected in the first round. If so, the incidence will fall in the follow-up, which may be erroneously interpreted as ascertainment bias in the first round. Another problem is that women of different ages have lived different parts of their risk periods, which influences the risk for disease derived by the selection criteria (daughters of gene carriers are supposed to be born with 50% risk of being carriers, while at the age of 70 years some carriers are dead of cancer giving a lower carrier risk to those alive). This argument lowers the expectations. It should also be mentioned that the penetrance(s) of the putative gene(s) may be higher than expected in the age group studied, leading to higher expectations of disease in gene carriers of a certain age.

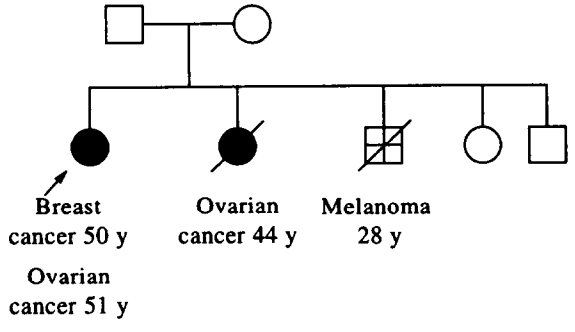
Our present position is that premenopausal patients with breast cancer in breast/ovarian cancer families should be considered for therapeutic oophorectomy, when the breast cancer is oestrogen-receptor positive. These women are almost certainly gene carriers, and the decision for oophorectomy is left to the patient and her surgeon after genetic counselling. It may also be hard to find arguments against oophorectomy in postmenopausal women in these families [26, 27]. A few cases of carcinomatosis following prophylactic oophorectomy have been reported [27].

We diagnosed 5 patients with ovarian cancer FIGO stage I and II with good prognoses, and 4 in stage III (Table 3). Although the numbers are small, this seems better than the general clinical situation where more than 60% of the patients have widespread disease (stage III–IV) at the time of diagnosis. However, it is the continuous follow-up of the cohort which will provide information on whether early diagnosis and treatment is a safe alternative to prophylactic oophorectomy in these families.

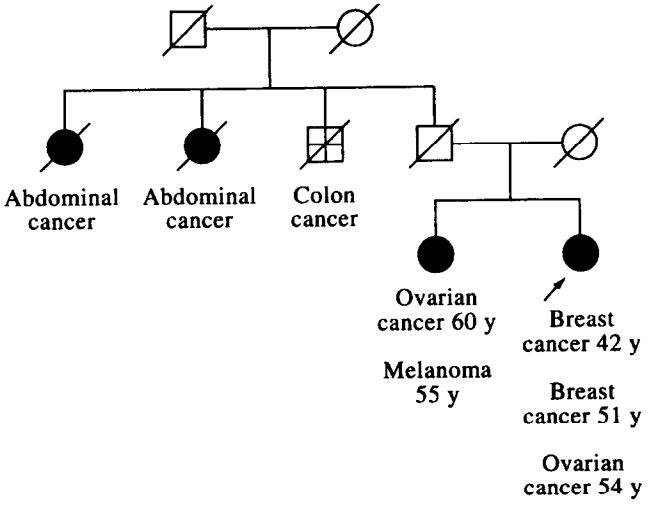
APPENDIX

Relevant part of pedigrees in families where ovarian cancer was prospectively demonstrated. All diagnoses were histologically verified. The proband (woman with prospectively demonstrated ovarian cancer) is indicated by an arrow. □, ○, unaffected male/female; ■, ●, breast/ovarian cancer; ⊞, ⊕, other cancer; ⊠, ∅, dead. Age at diagnosis shown. Number within symbol = number of sisters or brothers. y, years.

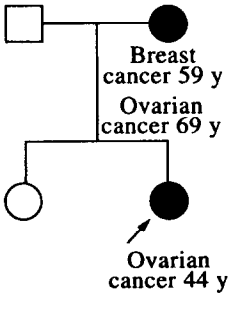
(a) Case 1 (Family DNR 839)



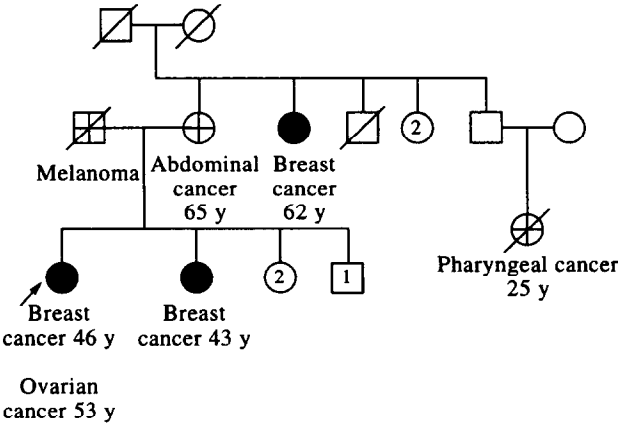
(b) Case 2 (Family DNR 128)

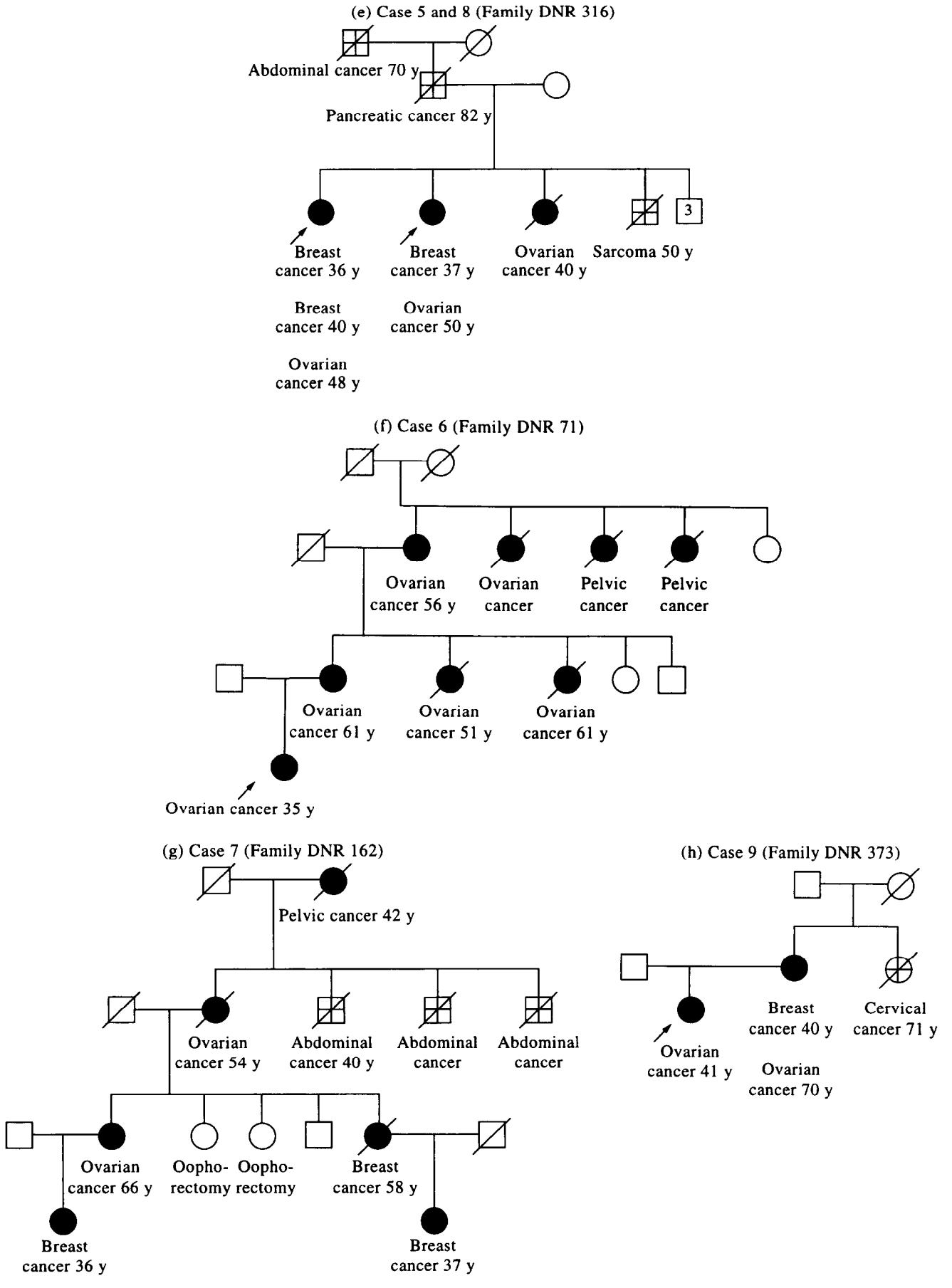


(c) Case 3 (Family DNR 220)



(d) Case 4 (Family DNR 155)




(e) Case 5 and 8 (Family DNR 316)
Abdominal cancer 70 y
Pancreatic cancer 82 y
3
Breast cancer 36 y
Breast cancer 37 y
Ovarian cancer 40 y
Sarcoma 50 y
Breast cancer 40 y
Ovarian cancer 50 y
Ovarian cancer 48 y
(f) Case 6 (Family DNR 71)
Ovarian cancer 56 y
Ovarian cancer
Pelvic cancer
Pelvic cancer
Ovarian cancer 61 y
Ovarian cancer 51 y
Ovarian cancer 61 y
Ovarian cancer 35 y
(g) Case 7 (Family DNR 162)
Pelvic cancer 42 y
Ovarian cancer 54 y
Abdominal cancer 40 y
Abdominal cancer
Abdominal cancer
Ovarian cancer 66 y
Oopho- rectomy
Oopho- rectomy
Breast cancer 58 y
Breast cancer 36 y
Breast cancer 37 y
(h) Case 9 (Family DNR 373)
Ovarian cancer 41 y
Breast cancer 40 y
Cervical cancer 71 y
Ovarian cancer 70 y

1. Young RC, Perez CA, Hoskins WJ. Cancer of the ovary. In DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*, 4th edn. Philadelphia, Lippincott Co, 1993, 1226–1263.
2. Engeland A, Haldorsen T, Tretli S, *et al.* Prediction of cancer incidence in the Nordic countries up to the years 2000 and 2010. *APMIS* 1993, **101** (Suppl. 38), 62.
3. Lynch HT, Bewtra C, Wells IC, Schuelke GS, Lynch JF. Hereditary ovarian cancer. In Lynch HT, Kullander S, eds. *Cancer Genetics in Women.* Boca Raton, CRC Press, 1987, Vol 1, 49–97.
4. Hall JM, Lee MK, Morrow J, *et al.* Linkage analysis of early onset familial breast cancer to chromosome 17q21. *Science* 1990, **250**, 1684–1689.
5. Miki Y, *et al.* A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* 1994, **266**, 66–71.
6. Easton DF, Ford D, Bishop DT, and the Breast Cancer Linkage Consortium. Breast and ovarian cancer incidence in BRCA1-mutation carriers. *Am J Hum Genetic* 1993, **56**, 265–271.
7. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE, and the Breast Cancer Linkage Consortium. Risks of cancer in BRCA1-mutation carriers. *Lancet* 1994, **343**, 692–695.
8. Cohen CJ, Jennings TS. Screening for ovarian cancer: the role of noninvasive imaging techniques. *Am J Obstet Gynecol* 1994, **170**, 1088–1094.
9. American College of Physicians. Screening for ovarian cancer: recommendations and rationale. *Ann Intern Med* 1994, **121**, 141–142.
10. DePriest PD, Van Nagell JR Jr, Gallion HH, *et al.* Ovarian cancer screening in asymptomatic postmenopausal women. *Gynecol Oncol* 1993, **51**, 12–20.
11. Droegemueller W. Screening for ovarian carcinoma: hopeful and wishful thinking. *Am J Obstet Gynecol* 1994, **170**, 1095–1098.
12. Granberg S, Wikland M. A comparison between ultrasound and gynecologic examination for detection of enlarged ovaries in a group of women at risk for ovarian cancer. *J Ultrasound Med* 1988, **7**, 59–64.
13. Bourne TH, Whitehead MI, Campbell S, Royston P, Bhan V, Collins WP. Ultrasound screening for familial ovarian cancer. *Gynecol Oncol* 1991, **43**, 92–97.
14. Bourne TH, Campbell S, Reynolds KM, *et al.* Screening for early familial ovarian cancer with transvaginal ultrasonography and colour blood flow imaging. *Br Med J* 1993, **306**, 1025–1029.
15. Muto MG, Cramer DW, Brown DL, *et al.* Screening for ovarian cancer: the preliminary experience of a familial ovarian cancer center. *Gynecol Oncol* 1993, **51**, 12–20.
16. Grover S, Quinn MA, Weideman P. Patterns of inheritance of ovarian cancer. An analyses from an ovarian cancer screening program. *Cancer* 1993, **72**, 526–530.
17. Karlan BY, Raffel LJ, Crvenkovic G, *et al.* A multidisciplinary approach to the early detection of ovarian carcinoma: rationale, protocol design, and early results. *Am J Obstet Gynecol* 1993, **169**, 494–500.
18. Møller P. Genetic cancer: a challenge and a possible strategy. *J Cancer Care* 1993, **2**, 94–99.
19. Granberg S. Ultrasonographic diagnoses and treatment of ovarian cysts. In Rulin MC, ed. *Clinical Obstetric and Gynecology.* Philadelphia, Lippincott, 1993, 363–374.
20. Nilsson O, Jansson EL, Dahlen U, Nilsson K, Nustad K, Lindholm L. New monoclonal antibodies for determination of the ovarian cancer associated antigen CA 125. In Klapdor R, ed. *Current Tumour Diagnosis: Applications, Clinical Relevance, Research, Trends.* Munchen, W. Zuckschwerdt Verlag GmbH 1994, 401–405.
21. Serov SF, Scully RE, Sobin LH. Histological typing of ovarian tumors. In *International Histological Classification of Tumors*, No 9. Geneva, World Health Organization, 1973, 17.
22. Saetersdal A, Dørum A, Heimdal K, *et al.* Early diagnosis of inherited breast cancer. *Anticancer Res*, in press.
23. Amos CI, Shaw GL, Tucker MA, Hartge P. Age at onset for familial ovarian cancer. *JAMA* 1992, **268**, 1896–1899.
24. Mann WJ, Patsner B, Cohen H, Loesch M. Preoperative serum Ca-125 levels in patients with surgical stage I invasive ovarian adenocarcinoma. *J Natl Cancer Inst* 1988, **80**, 208.
25. Salazar H, Godwin AK, Daly M, Hogan M, Rosenblum N, Hamilton TC. Characterization of early benign and malignant ovarian neoplasms in prophylactic oophorectomy. *Int J Gynecol Cancer* 1993, **3** (Suppl.), 40.
26. Cornelis RS, Cornelisse CJ, Devilee P. Selection of families for predictive testing for breast cancer. *Lancet* 1994, **344**, 1151–1152.
27. Meijer WJ, Van-Lindert AC. Prophylactic oophorectomy. *Eur J Obstet Gynecol Reprod Biol* 1992, **47**, 59–65.

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