Ovarian cancer in Western Australia, 1982–98: A population-based review of the trends and outcomes

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Abstract

Objectives

To investigate the incidence and mortality trends in ovarian cancer; review the utilisation of surgical procedures for the management of the disease and estimate relative survival in women diagnosed with ovarian cancer in Western Australia (WA) in the period 1982–98.

Case selection and methods

The WA Data Linkage System was used to identify 1,336 women diagnosed with malignant, primary ovarian cancer in the WA Cancer Registry; 77% of these women underwent a primary surgical procedure (n=1,126). Age-standardised rates were calculated by the direct method and time trends analysed by Poisson regression. Logistic regression examined the likelihood of having a surgical procedure in the periods 1988–93 and 1994–987 compared with 1982–87. Relative survival was used to compare patient survival with the general female population.

Results

The mean age of women diagnosed with ovarian cancer was 62 years (SD \pm 15). The age-specific incidence rate increased sharply from 7.6 per 100,000 woman-years at ages 40–44 years to 44.1 per 100,000 woman-years at 80–84 years. Similarly, the age-specific mortality rate increased from 2.3 to 46.2 per 100,000 woman-years at 40–44 and 80–84 years, respectively. The average incidence rate was 8.2 per 100,000 woman-years and decreased an average 1.08% per year; the decrease was restricted to women aged 45–64 years. The average mortality rate was 5.1 per 100,000 woman-years and remained stable over time, while a 1.2% per year increase was observed in 65–74 year-olds. Women with ovarian cancer were 3.7 times more

likely to have a bilateral salpingo-oophorectomy and 5 times more likely to have an omentectomy in 1994–98 compared with 1982–87. The median length of hospital stay was 14 days (IQR: 10–19); 21% were admitted as an emergency care; and in-hospital mortality was 4.4%. Thirty-four percent of women were readmitted within 30 days of separation from their primary surgery for chemo- or radiotherapy. Fiveyear relative survival was 38% overall and was 43% among women surgically treated; however there was a 15% increase in relative survival among those surgically treated from the period 1982–97 (38.8%) compared with 1994–98 (53.5%).

Conclusions

The incidence and mortality rates of ovarian cancer have remained relatively stable for the last two decades, whereas more women with ovarian cancer are receiving surgery today than they were 20 years ago. Women continue to be diagnosed at an advanced stage in the disease process, which limits treatment options for cure. With survival outcomes being poor in women with advanced disease the focus of management shifts to that of palliation instead of an intention to cure. An effective diagnostic technique is urgently required for detecting early, asymptomatic disease if there are to be real improvement in outcomes for women diagnosed with ovarian cancer.

Introduction

Ovarian cancer is the sixth most common cancer and the leading cause of death from a gynaecological malignancy in the world.¹ There is wide geographical variation in the incidence of ovarian cancer; rates are reported to be highest in Scandinavian countries (14.5–15.3 per 100,000 population), the United Kingdom (11.1 per 100,000 person-years) and North America (12.4 per 100,000 person-years).^{2–4} In Australia, the incidence rate of ovarian cancer was 9.0 per 100,000 population in 1998.⁵ China and Northern Africa have the lowest reported incidence rates (2.8 per 100,000 population).¹

The aetiology of ovarian cancer is poorly understood and most epidemiological studies have combined epithelial tumours as a whole, ignoring the existence of different histological types (serous, mucinous, endometrioid and clear cell). Several factors, including advanced age⁶, nulliparity^{2,7} and a family history of the disease^{6, 8, 9} have been associated with an increased risk of epithelial ovarian cancer, while oral contraceptives^{10–13}, tubal ligation and hysterectomy^{10, 14} have conferred a decreased risk.

The onset of ovarian cancer is insidious and often results in advanced disease at diagnosis. An estimated two-thirds of ovarian cancer tumours are in advanced stages at diagnosis.¹⁵ The late presentation is thought to reflect the fact that early disease is asymptomatic and when symptoms do develop they are non-specific. More than 50% of women diagnosed with ovarian cancer in Australia succumb to their disease within five years.

Surgery is a cornerstone in the primary management of ovarian cancer. The aim of surgery is to remove as much of the diseased tissue as possible, called debulking or cytoreduction of the tumour.⁶ The theoretical benefits of primary cytoreduction have been summarised by Griffiths.¹⁶ Cytoreductive surgery, in theory, should diminish affected areas with low vascularity and thereby enable chemotherapy to be administered more effectively. The literature suggests that a woman's survival is better when there is no mass of residual disease greater than 2cm after the primary surgery.^{17, 18}

The standard surgical procedures used in the primary management of ovarian cancer include bilateral salpingo-oophorectomy, total abdominal hysterectomy, infracolic omentectomy, and pelvic- and para-aortic lymphadenectomy.^{19–21} Women with metastatic disease at the time of primary surgery may also require gastrointestinal surgery.^{22, 23} Descriptors of the standard surgical procedures for ovarian cancer abound in the literature, however, information on the trends of these standard surgical procedures is lacking.

There is an increasing use of record linkage to evaluate the effectiveness and safety of treatment outcomes at the population level, because it has distinct advantages over methods involving selected case series based at one or more hospitals or clinics.^{24–26} The record linkage system in WA provides a mechanism that allows the clinical epidemiology, service utilisation and surgical outcomes of diseases to be assessed in a whole population, irrespective of health insurance status or the provider of care.^{27–29} The combination of a population-based record linkage system, the adequate (~1.9 million people) size and geographical isolation of the population of WA and the concentration of health services in the capital city of Perth provide an ideal research environment for the review of trends in surgical procedures for ovarian cancer in an entire community.

The present study used data from the WA Safety and Quality of Surgical Care Project³⁰, which was obtained from the WA Data Linkage System.³¹ The purpose of this study was to investigate the trends in incidence and mortality, to review the utilisation of surgical procedures used in the primary management of ovarian cancer and to estimate survival from the disease in Western Australia in the period 1982–98.

Patient selection and methods

The Western Australia Data Linkage System was used to relate patient records in the Hospital Morbidity Data System and Death Registry to all notifications of ovarian cancer in the WA Cancer Registry in the period 1982–98. The International Classification of Diseases (ICD–9, ICD–9-CM and ICD-Oncology) diagnosis codes were used to identify all women with a malignant neoplasm of the ovary.^{32–34} The ICD–9 and ICD–9-CM procedure codes used to identify patients surgically treated for ovarian cancer are summarised in Table 1. The linked data file was current at 27 March 2001.

All patients living in WA with a diagnosis of malignant, primary ovarian cancer in 1982–98 were eligible for inclusion in the study (n=1,455). Only those cases of ovarian cancer with pathology to support the diagnosis were included in the analysis (n=1,336). Only 77% (n=1,126) of the women diagnosed were found to have an admission for a primary surgical procedure in Western Australia.

The analysis was performed using SAS.35 Age-standardised rates of surgical procedures (per 100,000 woman-years) were calculated by the direct method³⁶ with the world standard population as the standard set of weights. The age groups were stratified by five-year intervals. The trend analysis was performed with Poisson regression and the significance of trends was determined by the likelihood ratio Chi-square test. Logistic regression was used to examine the likelihood of having a surgical procedure in the periods 1988-93 and 1994-98 compared with 1982-87. Relative survival analysis was performed using a SAS macro developed by Therneau et al. based on the Hakulinen method.^{37, 38} The computer program was modified to include annual life table data from the WA population in 1982-98, supplied by the Australian Bureau of Statistics. Differences between observed and expected survival were evaluated by the one-sample log-rank test. Follow-up time was calculated from the date of admission for the hospital episode in which the primary surgery took place to 31 December 1999. For those patients who died before this date the survival time was calculated from the date of admission to the date of death as specified on the death certificate. Relative survival was estimated at 30 days and 1, 3 and 5 years.

Results

There were 1,336 women diagnosed with primary, malignant ovarian cancer in Western Australia during the 17-year period. These women were a mean 62 years (SD±15) of age and were distributed similarly across socio-economic disadvantage quartiles (X^2 =76.53; df=3; p<0.0001) (Table 2). There were very few Aboriginal women with ovarian cancer; 44% of women had no private health insurance; and 59% were treated in a

public hospital. Almost one-half (45%) of the cases had serous tumours and 11% had mucinous tumours.

Incidence and mortality

The age-specific incidence and mortality rates increased with age. The incidence rate at ages 40-44 years was 7.6 per 100,000 woman-years, which rose to 28 per 100,000 woman-years at ages 55-59 years, and to 44.1 per 100,000 woman-years at ages 80-84 years. Similarly, the mortality rates were 2.3, 16.7 and 46.2 per 100,000 woman-years at ages 40-44, 55-59 and 80-84 years, respectively. The average incidence rate during the study period was 8.2 per 100,000 woman-years and decreased an average 1.08% per year (RR = 0.98; 95% CI: 0.978-1.00) (Figure 1). The decreasing incidence trend was restricted to women aged 45-54 years (0.38% per year; t = 2.34; p=0.03) and 55-64 years (1.3% per year; t = 3.68; p=0.002). The average mortality rate was 5.1 per 100,000 woman-years and remained stable over the study period (RR = 1.01; 95% CI: 0.99-1.03) (Figure 1), while a 1.2% per year increasing trend was observed in 65–74 year-olds (t = 3.16; p=0.007).

Relative survival

Relative survival at five years was 38% (95% CI: 35 - 41%) overall. Women who were surgically treated had better survival (43% at five years) than those who were not (18%); however, both groups had significantly worse survival than the general female population of Western Australia (Figure 2). Relative survival at five years increased 14.7% between the periods 1982–87 (38.8%) and 1994–98 (53.5%) (Figure 3).

Surgically treated patients

A total of 1,126 women (77% of all 1,336 women diagnosed) underwent a primary surgical procedure for ovarian cancer in Western Australia in 1982–98. The proportion of women receiving primary surgery varied across the time periods: 1982–87 (89.2%); 1988–93 (76.8%); and 1994–98 (87.8%). The median length of hospital stay was 14 days (IQR: 10–19). Women surgically treated were 11 years younger, on average, compared with patients who had no surgical treatment (F=1.25; df=1125; p=0.011). Twenty-one percent of patients were admitted as an emergency care and in-hospital mortality was 4.4%. Thirty-four percent of women were readmitted within 30 days of their primary surgery for chemotherapy or radiotherapy and an additional 32% were readmitted for other indications.

Trends in surgical procedures

There were 3,796 itemised surgical procedures performed for ovarian cancer in WA during the period 1982–98, of which 82% were carried out at the time of primary surgery (Table 3). The proportion of surgical procedures performed at the primary surgery greatly increased over the periods 1982–87 (26%), 1988–93 (34%) and 1994–98 (40%). A similar pattern was found for many individual surgical procedures. Women with ovarian cancer were four times more likely to receive a bilateral salpingo-oophorectomy, five times more likely to receive a lymphadenectomy in 1994–98 compared with 1982–87 (Table 4). Women were just as likely to have a total abdominal hysterectomy in 1994–98 as they were in 1982–87.

Trends in surgical procedures are shown in Figure 4. Omentectomy (RR=1.06; 95%CI: 1.04–1.08) and bilateral salpingo-oophorectomy (RR=1.06; 95%CI: 1.04–1.08) rates both increased an average 6% per year; however, total abdominal hysterectomy procedures showed no such trend. Lymphadenectomy increased an average 21% per year (RR=1.21; 95%CI: 1.17–1.25). The procedure rate for resection of the small bowel (RR=1.08; 95% CI: 1.02–1.14) showed the highest average increase per year (8%). Resection of the rectum (RR=1.06; 95% CI: 1.01–1.11) had the next highest average increase at 6%, followed by resection of the large bowel (RR=1.05; 95% CI: 1.02–1.08) at 5% per year.

Discussion

The present study showed that there has been little change in the incidence and mortality rates of ovarian cancer in Western Australia despite significant changes in diagnostic and surgical technology in the last 20 years. Surgical intervention, on the other hand, has significantly increased in the last 20 years. The most dramatic shift in surgical practice was found in lymphadenectomy, such that women were 17-times more likely to have this procedure in 1994–98 than they were in 1982–87. The disease is generally at an advanced stage when diagnosed, which limits treatment options intended to cure. Relative survival at five-years was only 38% overall and was 54% among patients surgically treated for the disease.

There are notable differences in the incidence and mortality rates reported here compared with North American, Scandinavian and Asian countries, which highlights the geographic variability of ovarian cancer. Trends in the rates observed here also vary from those reported overseas. The United States, Denmark and Sweden have all reported increasing trends in the incidence rate.³⁹⁻⁴¹ The stable mortality rate in Western Australia is consistent with the trends reported by the Netherlands and Sweden, while the United States reported a decreasing trend in its mortality rate.^{4, 39} Parity, oral contraceptive use, and bilateral oophorectomy are all protective factors for ovarian cancer and their trends have been shown to coincide with trends in the incidence of ovarian cancer.^{2, 10, 11, 42-45} The variation reported in incidence trends may be due, in part, to different trends in parity, oral contraceptive use, and bilateral oophorectomy in these countries compared with Australia.

Relative survival at five years was only 38%, which is similar to estimates reported in other Australian states.⁴⁶⁻⁴⁸ In contrast to Australian estimates, the United States reported the highest five-year relative survival (52%), however, we should interpret this figure cautiously, as it is the practice of the SEER program to include borderline malignant neoplasms in their survival

analysis.³⁹ Without the inclusion of borderline tumours the overall survival in the United States would be reduced considerably.

The observed trends in surgical intervention may be partly related to the increase in the number of specialist gynaecological oncologists who surgically manage this disease in WA. Since 1986, there have been two specialists practicing in Western Australia and a third joined the group in 1996. Compared with general surgeons and gynaecologists, gynaecological oncologists are more likely to achieve optimal cytoreduction as they have the training needed to manage ovarian tumours that spread beyond the true pelvis to surrounding tissue.^{49–51} In a validation study of ovarian cancer cases at King Edward Memorial Hospital it was found that these gynaecological oncologists achieved less than 1cm of residual disease in 73% (124/169) of women treated at King Edward Memorial Hospital in the period 1995–98.⁵²

A central issue that remains unresolved is whether it is the biologic behaviour of the tumour that allows optimal cytoreduction and prolonged survival, or whether the surgical intervention has an independent effect.53 The amount of residual disease from the primary cytoreductive surgery is a known prognostic factor for ovarian cancer.¹⁷ The 15% increase that we observed in survival between the periods 1982-87 and 1994–98 might be due, in part, to the ability of the specialists to achieve optimal cytoreduction (less than 1.5-2 cm residual disease) in the majority of their patients. Unfortunately, we cannot determine from our study whether the effect of surgical intervention on survival was independent of the tumours' biological behaviours. We also do not know the impact of chemotherapy and other treatments on patient survival in this study. Brun et al reported a 47-70% reduction in mortality in patients with a specific chemotherapy regimen compared with patients who did not receive chemotherapy.54 Further investigation is needed to assess the impact of chemotherapy on patient survival from ovarian cancer.

In addition to survival as an indicator of patient outcome, we also examined length of hospital stay, in-hospital mortality and readmission within 30 days of separation from hospital episode for primary surgery. The mean length of hospital stay was 14 days; however, the national average in 1993–97 was only 7 days.⁵⁵ The difference between the Western Australia and the national average was expected as the hospital episodes included in the calculation of hospital stay were different. In this study, we focused on the length of stay in hospital for only the primary surgery. The national average includes any hospital episode related to ovarian cancer, including same-day services such as chemotherapy and radiotherapy. The national average could therefore underestimate the length of stay women with ovarian cancer spend in hospital for their primary surgery.

Estimates of in-hospital mortality vary between 1–14% and have only been based on data from single institutions.^{56, 57} The 4.4% in-hospital mortality reported here is within the range already mentioned, but it may be a more precise estimate of in-hospital mortality due to ovarian cancer, because it is based on population data and not on a single hospital subset. The 30-day readmission risk was 66% overall, but 34% were read-

mitted in 30 days for chemotherapy or radiotherapy. An additional 32% of women were readmitted for reasons unrelated to chemotherapy or radiotherapy. There is little information in the literature regarding risks of 30-day readmission following the primary surgery for ovarian cancer. The available estimates range from 5–64%, but pertain to adhesion-related readmissions and readmissions following gastrointestinal surgery for ovarian cancer.^{58, 59}

A surprising result was the 14% five-year survival observed in women who did not undergo surgery to manage the disease. For a woman with ovarian cancer not to undergone surgical treatment suggests that the disease would have been advanced (FIGO stage IIIc or IV) when diagnosed and palliation was the intended basis of treatment. This figure is consistent, however, with reports of 7-24%^{17, 48, 60} relative survival in women with advanced disease; but it raises concern that borderline malignant tumours are also being recorded as malignant in the cancer registry. Ovarian borderline malignant tumours were first described in 1929, but this group was not accepted as a separate entity by FIGO and the World Health Organisation until the early 1970s.⁶¹⁻⁶³ The "borderline" terminology replaced ovarian lesions previously diagnosed partly as "cystadenoma with atypia" and partly as "carcinoma".64 Intraobserver reproducibility in the classification of malignant and borderline ovarian tumours in the Norwegian Cancer Registry was reported at 62% (kappa = 0.53), with a range of 50-75% for individual pathologists.⁶⁵ It is unknown when ovarian tumours began to be classified as 'borderline' malignant tumours in Western Australia. As a consequence, the long-term survival in women not receiving surgical treatment may be over-estimated in this study.

The potential for selection bias in this study population was reduced by using population-based data to identify all cases of ovarian cancer in the community as distinct from a subset from a single institution. Loss to follow-up due to people leaving the state must be considered in this type of population study. Given the geographical isolation of the state, one would expect this to have been uncommon occurrence in the age group involved in the study. It has been established that 1.7% of the population over 18 years of age leave Western Australia permanently each year, and it may be less than 1% in a cohort situation.^{29–31}

In conclusion, ovarian cancer incidence and mortality rates in Western Australia have shown little variation, where as more women are receiving surgery today than they were 20 years ago. Women continue to be diagnosed late in the disease process when treatment options for cure are limited, as was shown by the 38% relative survival at five-years. These results are encouraging; however, it is clear that an effective diagnostic technique for detecting early, asymptomatic disease needs to be developed if a real impact is to be made on the outcomes of treatment in all women diagnosed with ovarian cancer. As molecular techniques such as proteomic analysis^{66–68} and DNA microarrays^{69–71} are refined, the identification of new diagnostic markers and the classification of tumours for ovarian cancer are likely to improve.

Surgical Procedures	ICD-9 Codes	ICD-9-CM Codes
Hysterectomy	5-682 to 5-687	68.3 to 68.9
	5-651 to 5-655	65.23, 65.25, 65.29, 65.3,
		65.4, 65.51, 65.52, 65.61,
Oophorectomy		65.62
Omentectomy	5-543	54.4
	5-401 thru 5-404	40.24, 40.29, 40.3
		40.50, 40.52-40.54,
Lymphadenectomy		40.59
	5-455, 5-456	45.70 - 45.76, 45.79,
Resection of large bowel		45.80
Resection of small bowel	5-454	45.60 - 45.63
	5-483 thru 5-485	48.49, 48.5, 48.62- 48.63,
Resection of rectum		48.69
Intestinal anastomosis	5-457,5-458, 5-459	45.90 - 45.95
	5-461, 5-462, 5-463,	46.10 - 46.14, 46.20 -
Colostomy	5-465	46.24, 46.32
Gastrostomy	5-431	43.10, 43.11, 43.19
Excision of abdominal wall (lesion)	5-541	54.3
Appendectomy	5-470	47.0-47.1

Table 1 ICD-9 and ICD-9-CM procedure codes used to identify women surgically treated for ovarian cancer

Characteristic	N=1336	
Age (years)		
Mean (STD)	62 (15)	
Median (IQR)	63 (52-73)	
Race		
Aboriginal	15 (1%)	
Non-Aboriginal	1321 (99%)	
Tumour Histology		
Epithelial tumours	1208 (90%)	
Serous	597 (45%)	
Mucinous	153 (11%)	
Endometrioid	107 (8%)	
Clear Cell	62 (5%)	
Other and unspecified	289 (22%)	
adenocarcinoma		
Sex cord/stromal	55 (4%)	
Germ cell	40 (3%)	
Other tumours	33 (2%)	
Socio-economic disadvantage ¹		
Most Disadvantaged	316 (24%)	
More Disadvantaged	326 (25%)	
Less Disadvantaged	299 (23%)	
Least Disadvantaged	364 (28%)	
Type of health insurance		
No private health insurance	584 (43.7%)	
Private health insurance	521 (38.9%)	
Unknown	231 (17.3%)	
Type of treating hospital		
Public	794 (59.4%)	
Private	332 (24.9%)	
Unknown	210 (15.7%)	

Table 2 Characteristics of women with ovarian cancer in Western Australia (1982–98) ¹43 missing postcodes; n=1305

Australia, 1982-98.				
	Primary Surgery	Subsequent Surgery	Total Procedures	Rate of Surgical
	(n = 3133)	(n = 663)	(n = 3796)	Procedures ^{a,b}
Hysterectomy (total)	626 (20%)	66 (10%)	692 (18%)	4.7
Subtotal abdominal hysterectomy	12	1	13	0.1
Total abdominal hysterectomy	472 (15%)	48	520 (14%)	3.5
Vaginal hysterectomy	4	3	7	0
Radical abdominal hysterectomy	121	11	132	0.9
Radical vaginal hysterectomy	1	0	1	0
Hysterectomy not otherwise	16	3	19	0.1
specified				
Oophorectomy (total)	1007 (32%)	83 (13%)	1090 (29%)	7.5
Partial oophorectomy	153	14	167	1.1
Unilateral oophorectomy	113	15	128	0.8
Unilateral salpingo-oophorectomy	96	22	118	0.7
Bilateral oophorectomy	74	5	79	0.6
Bilateral salpingo-oophorectomy	571 (18%)	27	598 (16%)	4.3
Gastrointestinal (total)	410 (13%)	218 (33%)	628 (17%)	3.1
Large bowel resection	177 (6%)	50	227 (6%)	1.3
Small bowel resections	55	44	99	0.4
Resection of the rectum	82	28	110	0.6
Intestinal anastomosis	68	45	113	0.5
Colostomy	23	30	53	0.2
Gastrostomy	5	21	26	0
Other procedures				
Omentectomy	608 (19%)	122 (18%)	730 (19%)	4.5
Lymphadenectomy	217 (6%)	63	280 (7%)	1.6
Excision of abdominal wall lesion	168	94 (14%)	262	1.2
Appendectomy	97	17	114	0.7

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Table 3 Crude number and average rate of surgical procedures performed for ovarian cancer in Western Australia, 1982–98

^aAverage rates are based on procedures performed at the primary surgery.

^bRates expressed per 100,000 woman-years.

Procedure	1988-93	p-value	1994-98	p-value
	OR (CI)		OR (CI)	
Total abdominal hysterectomy	1.49 (1.12-1.99)	0.0068	0.99 (0.74-1.33)	0.9590
Bilateral salpingo-oophorectomy	2.71 (2.01-3.65)	< 0.0001	3.72 (2.75-5.03)	< 0.0001
Omentectomy	3.03 (2.24-4.09)	< 0.0001	5.13 (3.76-6.99)	< 0.0001
Lymphadenectomy	6.79 (3.29-13.96)	< 0.0001	16.71 (8.32-33.55)	< 0.0001
Large bowel resection	2.76 (1.75-4.33)	< 0.0001	1.81 (1.13-2.91)	0.0139
Small bowel resection	2.03 (0.90-4.59)	0.0872	2.97 (1.37-6.43)	0.0057
Rectal resection	2.07 (1.09-3.91)	0.0253	2.49 (1.34-4.65)	0.0038

Table 4 The odds of a woman with ovarian cancer having a surgical procedure in the periods 1988–93 and 1994–98 compared with 1982–87



Figure 1 Age-standardised incidence and mortality rates of ovarian cancer in Western Australia



Figure 2 Relative survival of ovarian cancer patients who underwent surgical treatment compared with those who had no surgical treatment in Western Australia, 1982–98



Figure 3 Relative survival for three time periods



Figure 4 Trends in surgical procedures

References

1 Parkin DM, Pisani P, Ferlay J. Global cancer statistics. CA Cancer J Clin 1999;49(1):33–64.

2 Parazzini F, Franceschi S, La Vecchia C, Fasoli M. The epidemiology of ovarian cancer. Gynecol Oncol 1991;43(1):9–23.

3 Whelan SL, Parkin DM, Masuyer E. Patterns of Cancer in Five Continents. IARC Scientific Publications No.102. Lyon, France: International Agency for Research on Cancer (WHO); 1990.

4 Gonzalez-Diego P, Lopez-Abente G, Pollan M, Ruiz M. Time trends in ovarian cancer mortality in europe (1955–1993). Effect of age, birth cohort and period of death. Eur J Cancer 2000;36(14):1816–24.

5 Australian Institute of Health and Welfare (AIHW), Australasian Association of Cancer Registries (AACR). Cancer in Australia 1998. AIHW cat. no. CAN 12. Canberra: AIHW (Cancer Series no. 17); 2001.

6 Partridge E, Barnes M. Epithelial ovarian cancer: prevention, diagnosis, and treatment. CA Cancer J Clin 1999;49:297–320.

7 Daly M, Obrams GI. Epidemiology and risk assessment for ovarian cancer. Semin Oncol 1998;25(3):255–64.

8 Schildkraut JM, Thompson WD. Familial ovarian cancer: a populationbased case-control study. Am J Epidemiol 1988;128(3):456-66.

9 Schildkraut JM, Thompson WD. Relationship of epithelial ovarian cancer to other malignancies within families. Genet Epidemiol 1988;5(5):355–67.

10 Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. IV. The pathogenesis of epithelial ovarian cancer. Collaborative Ovarian Cancer Group. Am J Epidemiol 1992;136(10):1212–20.

11 Whittemore AS. Characteristics relating to ovarian cancer risk: implications for prevention and detection. Gynecol Oncol 1994;55(3 Pt 2):S15–9.

12 Purdie D, Green A, Bain C, Siskind V, Ward B, Hacker N, Quinn M, Wright G, Russell P, Susil B. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group. Int J Cancer 1995;62(6):678–84.

13 Kelsey JL, Whittemore AS. Epidemiology and primary prevention of cancers of the breast, endometrium, and ovary. A brief overview. Ann Epidemiol 1994;4(2):89–95.

14 Green A, Purdie D, Bain C, Siskind V, Russell P, Quinn M, Ward B. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group. Int J Cancer 1997;71(6):948–51.

15 Kristensen GB, Trope C. Epithelial ovarian carcinoma. Lancet 1997;349(9045):113-7.

16 Griffiths CT. Surgery at the time of diagnosis in ovarian cancer. In: Black-ledge G, Chan KK, editors. Management of ovarian cancer. London: Butterworth and Co.; 1986. p. 60–75.

17 Pecorelli S, Odicino F, Maisonneuve P, Creasman WT, Shepherd JH, Sideri M, Benedet JL. FIGO annual report on the results of treatment in gynaecological cancer: carcinoma of the ovary. J Epidemiol Biostat 1998;3(1):75–102.

18 Friedlander ML. Prognostic factors in ovarian cancer. Semin Oncol 1998;25(3):305-14.

19 Benedet JL, Bender H, Jones H, 3rd, Ngan HY, Pecorelli S. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet 2000;70(2):209–62.

20 Nunns D, Symonds P, Ireland D. Surgical management of advanced ovarian cancer [Review]. Obstetrical & Gynecological Survey 2000;55(12):746–751.

21 Stratton JF, Tidy JA, Paterson MEL. The surgical management of ovarian cancer [Review]. Cancer Treatment Reviews 2001;27(2):111–118.

22 Dauplat J, Le Bouedec G, Pomel C, Scherer C. Cytoreductive surgery for advanced stages of ovarian cancer. Semin Surg Oncol 2000;19(1):42–8.

23 Lichtenegger W, Sehouli J, Buchmann E, Karajanev C, Weidemann H. Operative results after primary and secondary debulking-operations in advanced ovarian cancer (AOC). J Obstet Gynaecol Res 1998;24(6):447–51.

24 Leibson CL, Ballard DJ, Whisnant JP, Melton LJ, 3rd. The compression of morbidity hypothesis: promise and pitfalls of using record-linked data bases to assess secular trends in morbidity and mortality. Milbank Q

1992;70(1):127-54.

25 Sibthorpe B, Kliewer E, Smith L. Record linkage in Australian epidemiological research: health benefits, privacy safeguards and future potential. Aust J Public Health 1995;19(3):250–6.

26 Simunovic M, To T, Johnston KW, Naylor CD. Trends and variations in the use of vascular surgery in Ontario. Can J Cardiol 1996;12:249–53.

27 Semmens JB, Wisniewski ZS, Bass AJ, Holman CD, Rouse IL. Trends in repeat prostatectomy after surgery for benign prostate disease: application of record linkage to healthcare outcomes. BJU Int 1999;84(9):972–5.

28 Semmens JB, Norman PE, Lawrence-Brown MM, Bass AJ, Holman CD. Population-based record linkage study of the incidence of abdominal aortic aneurysm in Western Australia in 1985–1994. Br J Surg 1998;85(5):648–52.

29 Semmens JB, Platell C, Threlfall TJ, Holman CD. A population-based study of the incidence, mortality and outcomes in patients following surgery for colorectal cancer in Western Australia. Aust N Z J Surg 2000;70(1):11–8.

30 Semmens JB, Lawrence-Brown MM, Fletcher DR, Rouse IL, Holman CD. The Quality of Surgical Care Project: a model to evaluate surgical outcomes in Western Australia using population-based record linkage. Aust N Z J Surg 1998;68(6):397–403.

31 Holman CD, Bass AJ, Rouse IL, Hobbs MS. Population-based linkage of health records in Western Australia: development of a health services research linked database. Aust N Z J Public Health 1999;23(5):453–9.

32 World Health Organisation. ICD–9:International Classification of Diseases. Manual of the international statistical classification of diseases and related health problems. Geneva: WHO; 1977.

33 World Health Organisation. ICD–9-CM:International classification of diseases. Manual of the international statistical classification of diseases, injuries, and causes of death: clinical modifications. Geneva: WHO; 1986.

34 World Health Organisation. ICD-O:International classification of diseases for oncology. 2nd ed. Geneva: WHO; 1990.

35 SAS Institute Inc. SAS Release 8.0 Edition. In. Cary, NC: SAS Institute Inc.; 1999.

36 Rothman KJ. Modern Epidemiology. Boston: Little, Brown & Company; 1986.

37 Therneau T, Sicks R, Bergstralh E, Offord J. Expected Survival Based on Hazard Rates. Technical Report #52, Mayo Foundation 1994.

38 Hakulinen T, Tenkanen L, Abeywickrama K, Paivarinta L. Testing equality of relative survival patterns based on aggregated data. Biometrics 1987;43(2):313–25.

39 Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Edwards BK. SEER Cancer Statistics Review, 1973–1998. Bethesda, MD: National Cancer Institute; 2001.

40 Ewertz M, Kjaer SK. Ovarian cancer incidence and mortality in Denmark, 1943–1982. Int J Cancer 1988;42(5):690–6.

41 Adami HO, Bergstrom R, Persson I, Sparen P. The incidence of ovarian cancer in Sweden, 1960–1984. Am J Epidemiol 1990;132(3):446–52.

42 Weiss NS, Lyon JL, Liff JM, Vollmer WM, Daling JR. Incidence of ovarian cancer in relation to the use of oral contraceptives. Int J Cancer 1981;28:669–671.

43 Hartge P, Whittemore AS, Itnyre J, McGowan L, Cramer D. Rates and risks of ovarian cancer in subgroups of white women in the United States. The Collaborative Ovarian Cancer Group. Obstet Gynecol 1994;84(5):760–4.

44 Beard CM, Hartmann LC, Atkinson EJ, O'Brien PC, Malkasian GD, Keeney GL, Melton LJ, 3rd. The epidemiology of ovarian cancer: a population-based study in Olmsted County, Minnesota, 1935–1991. Ann Epidemiol 2000;10(1):14–23.

45 Melton LJ, 3rd. Bilateral oophorectomy trends in Olmsted County, Minnesota, 1950–1987. Epidemiology 1991;2(2):149–152.

46 Baade P, Coory M, Ring I. Cancer survival in Queensland 1982 to 1995. Brisbane: Health Information Centre, Queensland Health; 2000.

47 Coates M, Tracey E. Cancer in New South Wales, incidence and mortality 1997. Sydney: NSW Cancer Council; 2000.

48 South Australian Cancer Registry. Epidemiology of cancer in South Aus-

49 Junor EJ, Hole DJ, McNulty L, Mason M, Young J. Specialist gynaecologists and survival outcome in ovarian cancer: a Scottish national study of 1866 patients. Br J Obstet Gynaecol 1999;106(11):1130–6.

50 Eisenkop SM, Spirtos NM, Montag TW, Nalick RH, Wang HJ. The impact of subspecialty training on the management of advanced ovarian cancer. Gynecol Oncol 1992;47(2):203–9.

51 Nguyen HN, Averette HE, Hoskins W, Penalver M, Sevin BU, Steren A. National survey of ovarian carcinoma. Part V. The impact of physician's specialty on patients' survival. Cancer 1993;72(12):3663–70.

52 Laurvick CL. A population-based study of the trends and outcomes following a diagnosis of ovarian cancer in Western Australia, 1982–1998 [MPH Dissertation]. Perth: The University of Western Australia; 2001.

53 Covens AL. A critique of surgical cytoreduction in advanced ovarian cancer. Gynecol Oncol 2000;78(3 Pt 1):269–74.

54 Brun JL, Feyler A, Chene G, Saurel J, Brun G, Hocke C. Long-term results and prognostic factors in patients with epithelial ovarian cancer. Gynecol Oncol 2000;78(1):21–7.

55 Australian Institute of Health and Welfare (AIHW). Interactive National Hospital Morbidity Data. In: Australian Institute of Health and Welfare; 2000.

56 Clarke-Pearson DL, Chin NO, DeLong ER, Rice R, Creasman WT. Surgical management of intestinal obstruction in ovarian cancer. I. Clinical features, postoperative complications, and survival. Gynecol Oncol 1987;26(1):11–8.

57 Venesmaa P, Ylikorkala O. Morbidity and mortality associated with primary and repeat operations for ovarian cancer. Obstet Gynecol 1992;79(2):168–72.

58 Ellis H, Moran BJ, Thompson JN, Parker MC, Wilson MS, Menzies D, McGuire A, Lower AM, Hawthorn RJS, O'Brien F, Buchan S, Crowe AM. Adhesion-related hospital readmissions after abdominal and pelvic surgery: a retrospective cohort study. Lancet 1999;353(9163):1476–1480.

59 Tamussino KF, Lim PC, Webb MJ, Lee RA, Lesnick TG. Gastrointestinal surgery in patients with ovarian cancer. Gynecol Oncol 2001;80(1):79–84.

60 Allen DG, Coulter J. Survival of patients with epithelial ovarian cancer and the effect of lymphadenectomy in those with stage 3 disease. Aust N Z J Obstet Gynaecol 1999;39(4):420–4.

61 Ingelman-Sundberg A. Classification and staging of malignant tumors in the female pelvis. Acta Obstet Gynecol Scand 1971;50:1–7.

62 Serow SF, Scully RE, Sobin LH. Histologic typing of ovarian tumours. Geneva: World Health Organization; 1973.

63 Taylor HC. Malignant and semimalignant tumors of the ovary. Surg Gynecol Obstet 1929;48:204–230.

64 Bjorge T, Engeland A, Hansen S, Trope CG. Prognosis of patients with ovarian cancer and borderline tumours diagnosed in Norway between 1954 and 1993. Int J Cancer 1998;75(5):663–70.

65 Stalsberg H, Abeler V, Blom GP, Bostad L, Skarland E, Westgaard G. Observer variation in histologic classification of malignant and borderline ovarian tumors. Hum Pathol 1988;19(9):1030–5.

66 Petricoin EF, Ardekani AM, Hitt BA, Levine PJ, Fusaro VA, Steinberg SM, Mills GB, Simone C, Fishman DA, Kohn EC, Liotta LA. Use of proteomic patterns in serum to identify ovarian cancer. Lancet 2002;359(9306):572–7.

67 Brown Jones M, Krutzsch H, Shu H, Zhao Y, Liotta LA, Kohn E, Petricoin EF. Proteomic analysis and identification of new biomarkers and therapeutic targets for invasive ovarian cancer. Proteomics 2002;2:76–84.

68 Alaiya AA, Franzen B, Auer G, Linder S. Cancer proteomics: from identification of novel markers to creation of artifical learning models for tumor classification. Electrophoresis 2000;21(6):1210–7. [pii].

69 Golub TR, Slonim DK, Tamayo P, Huard C, Gaasenbeek M, Mesirov JP, Coller H, Loh ML, Downing JR, Caligiuri MA, Bloomfield CD, Lander ES. Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. Science 1999;286(5439):531–7.

70 King HC, Sinha AA. Gene expression profile analysis by DNA microar-

rays: promise and pitfalls. Jama 2001;286(18):2280-8.

71 Welsh JB, Zarrinkar PP, Sapinoso LM, Kern SG, Behling CA, Monk BJ, Lockhart DJ, Burger RA, Hampton GM. Analysis of gene expression profiles in normal and neoplastic ovarian tissue samples identifies candidate molecular markers of epithelial ovarian cancer. PNAS 2001;98(3):1176–1181.