HAEMOSTATIC STATUS IN PATIENTS WITH OVARIAN CANCER COMPARED WITH PATIENTS WITH BENIGN OVARIAN CYSTS AND THE STUDY OF THE RELATIONSHIPS BETWEEN HAEMOSTATIC LEVELS IN OVARIAN CANCER PATIENTS WITH KNOWN SURVIVAL OUTCOME

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Summary

Ovarian cancer is one of the more severe gynaecological malignancies known in women as it has a long asymptomatic course and usually presents at an advanced stage at time of diagnosis. The five-year survival rate is between 30% to 40%.

Sub-clinical abnormalities of haemostasis have been reported in cancer with an on-going low-grade disseminated intravascular coagulation. A comparative systemic study of 36 patients with preoperative ovarian cancer and 35 patients with benign ovarian cysts showed hypercoagulation, increased platelets, platelet activation and enhanced fibrinolysis in ovarian cancer. Elevated tissue-plasminogen activator (t-PA) antigen, plasminogen activator inhibitor-1 (PAI-1) antigen and urokoinase-like plasminogen activator receptor (u-PAR) were also seen. Tissue Factor Pathway Inhibitor (TFPI) which play a role in the inhibition of Tissue Factor induced coagulation were significantly raised in ovarian cancer patients compared to patients with benign ovarian cysts. In advanced ovarian cancer further enhanced thrombin generation were evident by significantly reduced antithrombin III (ATIII) levels and elevated D-dimer level indicating enhanced fibrinolysis.

There is increasing evidence to suggest associations between fibrinolytic system and cancer especially the primary tumour. In this study of 23 ovarian cancer and 18 ovarian benign tissue extracts, significant upregulation of u-PA antigen and PAI-1 antigen were seen in ovarian cancer compared with benign ovarian cysts. There were no significant differences between early stage and advanced stage of cancer in the fibrinolytic and inhibitor parameters studied, except increased t-PA activity level in advanced ovarian cancer. Furthermore,no significant association of haemostatic levels in primary tumour extracts with disease outcome was found when compared with

mortality with those still living past 36 months from disease. In the systemic circulation, haemostatic parameters studied were not correlated with disease outcome when mortality within 12 months, 24 months and 36 months were compared with those still living past 36 months except for clotting time, ATIII, plasminogen and D-dimer levels. Significant relationships of haemostatic parameters with age were seen in those above 50 years old who had higher levels of t-PA antigen and beta-thromboglobulin (ß-TG).

Fibrin zymography demonstrated the presence of single-chain t-PA and u-PA in both plasma and tissue extracts in benign cysts and ovarian cancer cohorts.

Out of the total of 38 patients with ovarian cancer recruited into the study, 16 patients died within 35 months from disease. The survival rate for ovarian cancer at 12 months was 66.7%, at 24 months 51.9% and 40.7% at 36 months. Eleven patients at the time of analysis is still living between 36 months and 59 months from the disease. Mortality was mainly due to advanced stage of cancer except one (Stage IC) who had other complications.

From this study it appears that survival outcome favours those with preoperative normal ATIII and D-dimer levels especially in early ovarian cancer and had chemotherapy. ATIII and D-dimer levels could be included with known FIGO (Federation of International Gynaecology and Obstetrics) stage prognosis as systemic prognostic markers for survival outcome at least for the first 36 months of disease. The outcome of this study justifies the concept of treating patients with anticoagulant drugs preferably low molecular weight heparin (LMWH) to improve the prognosis or the quality of life and this has been a subject of current concern internationally.

Chapter 1

The Epidemiology of Ovarian Cancer

Incidence and Mortality Trends

The Epidemiology of Ovarian Cancer

Cancer Aetiology

Aetiology and epidemiology are often associated with each other. Chemicals and radiation are two agents now clearly shown to cause cancers in humans whilst viruses are highly suspect on the basis of our present knowledge. The objective of cancer aetiology is cancer prevention.

1.1.1 Cancer Epidemiology

Epidemiological research has strongly suggested that variations in social habits and exposure to environmental agents have led to variations in the incidence of cancers among the various groups of population. The relationship between man and his environment and the long latent period of cancer development has contributed to the complexity and identification of cancer inducing factors difficult (Barber 1992).

Ovarian cancer is an important cause of morbidity and mortality, especially in middle-aged women. It is the sixth most common site of cancers in women after breast, lung, colon, rectum and endometrium (Harlap 1993). Ovarian cancer affects about 4% of half a million women diagnosed each year with cancer in the United States (National Cancer Institute 1989) and between 3 and 7% of women in other countries (Parkin et al 1988). The great majority of ovarian cancers are epithelial in origin with incidence increased sharply and peaks at ages 65 to 75 years whilst the uncommon germ-cell tumours showed peak incidence in women aged between 15 and 34 years.

The precise cause of epithelial ovarian cancer estimated to account for 80 to 90% of all ovarian carcinomas (Baylis et al 1986) is not known but a number of epidemiologic factors have been suggested to be associated with ovarian cancer.

Among them are nulliparity, infertility, marked premenstrual strain, abnormal breast swelling, marked dysmenorrhoea, increased abortion rate, early menopause, group A blood, irradiation of pelvic organs, environmental factors, industrial products, socio-economic status, celibacy, breast cancer and resistant to mump parotitis (Barber 1992). In epithelial ovarian cancer, circumstantial evidence suggested by the reproductive profile of women at highest risk indicates that repititive ovulation is involved in the pathophysiology of the disease. A novel hypothesis suggesting that inflammation is the common mechanism underlying this disease (Ness & Cottreau 1999). Pregnancy and the use of oral contraceptive pill seem to have a protective effect for ovarian cancer was reported (Joly DJ et al 1974; McGowan et al 1979; Hildreth NG et al 1981; Rosenbergh et al 1982; Risch et al 1983) and also for parity (Negri et al 1991).

1.1.2 Incidence and Trends

The annual incidence of ovarian cancer varies considerably throughout the world. The highest rates are found in industrialised countries except Japan. In Scandinavian countries the incidence was between 13.9 and 15.3/100,000 women per year (Muir et al 1987), whereas in Miyagi, Japan it was 3.2/100,000 (Lingeman 1983). However, residents from low incidence countries like Japan who migrated to the United States develop a risk similar to that of native-born Americans after living in the United States for one to two generations (Buell & Dunn 1965; Haenszel & Kukihara 1968) suggesting the important contribution of environmental factors. In Europe, a north to south gradient age-adjusted incidence from Scandinavian countries to intermediate incidences in the United Kingdom, France, Switzerland and Germany of between 7.8 and 13.2/100,000 women and countries bordering the Mediterranean, the incidence

was between 5.4 and 11.7/100,000. In the Netherlands it was 14.9/100,000 between 1989 and 1991 and decreased to 11.4/100,000 in the period 1989 to 1993 (Koper et al 1996). Similarly in Norway, the incidence of ovarian cancer rose until mid-1980s and stabilized thereafter (Bjorge et al 1997). A reverse trend of incidence from south to north gradient was seen in South America (Parkin et al 1988). In the United States, the annual incidence is 12-13 per 100,000 women which is similar to Canada (Muir et al 1987, Ayiomamitis 1989). Among Chinese women, ovarian cancer was documented as 5.0 and 5.8 /100,000 in Shanghai and Hong Kong respectively, and 8.5/100,000 in the Chinese in San Francisco compared to the Bay Area Caucasians' of 12.9/100,000 (Muir et al 1987). In the United States, the age-adjusted incidence of ovarian cancer in 1987-1991 was 14.8/100,000 (Ries et al 1998). The incidence was higher in whites compared to blacks and the differences diverge progressively with increasing age (National Cancer Institute 1989). Asian-American women were lowest among Native American women (Ries et al 1998). Blacks showed incidence of higher rates of ovarian cancer than whites below 45 years of age (Weiss et al 1977). In Israel, the incidence of ovarian cancer in Jewish emigrants from Europe and the Americas is among the highest in the world (Parkin 1989; Steinitz et al 1989), with European-born Jews having an incidence rate of 17.2/100,000 (Roush et al 1987). In contrast, the Jewish emigrants from North Africa and Asian near East region where fertility is high is associated with lower incidence of the disease (Steinitz et al 1989). The age-standardized annual incidence rate of ovarian cancer in the five continents between 1988 and 1992 is shown in Table 1-1 and the worldwide burden of cancer in females in developed and developing countries in Fig 1.1-1.

Worldwide Burden of Cancer in Females in Developed and Developing countries.

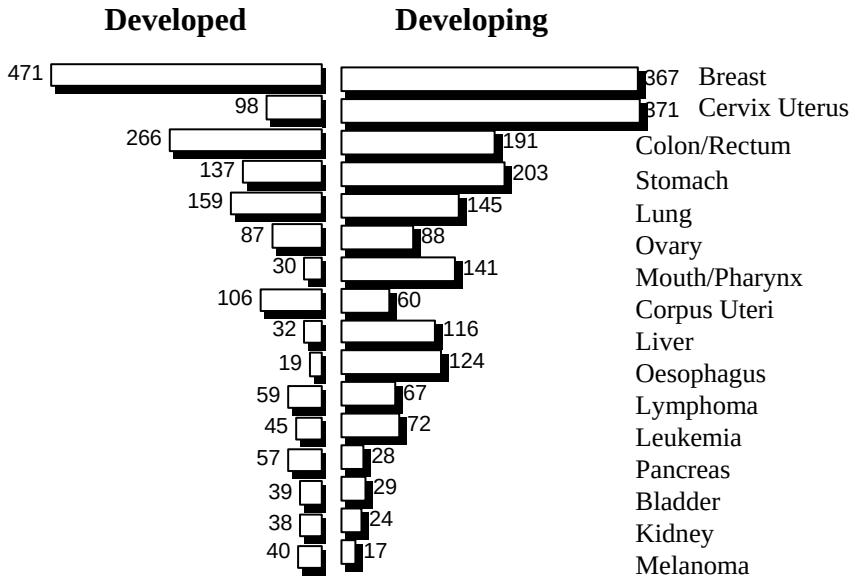


Fig. 1.1-1. ***Estimated numbers of cancer cases (1000s) in females by site around 1990****.(Parkin et al 1997, WHO-IARC Biennial Report 1996-1997, Lyon France 1997).*

The above figures showed estimates of incidence around 1990 of cancer site and level of development. In women, breast and colorectal cancer are still first and second in developed countries and in developing countries, the formerly most common site, the cervix, is now parallel by cancer of the breast.

Table 1.1-1. *The annual age-standardized incidence rate (per 100,000) of ovarian cancer of selected countries in the five continents between 1988 and 1992.*

	No. (all ages)	ASR
Africa:		
Uganda Kyadondo	48	6.6
Americas: Central and South		
Argentina, Concordia	26	7.6
Brazil, Porto Alegre	183	8.4
Colombia, Cali	268	8.9
Costa Rica	330	5.9
Ecuador, Quito	146	6.3
Peru, Lima	296	6.0
Uruguay, Montevideo	300	9.8
North America		
Canada	9793	10.5
Canada, Yukon	17	19.9
US, San Francsico Bay Area		
(*non-Hispanic white*)	1164	13.2
(*Hispanic –white*)	109	9.9
(*Black)*	125	9.5
(*Chinese*)	66	7.8
(*Japanese*)	16	7.4
US, Iowa	1359	12.0
US, Conneticut *White*	1383	11.6
Black	47	7.0
Europe		
Austria, Tyrol	366	15.1
Czech Republic	5082	13.3
Denmark	2874	14.0
Finland	2656	10.9
France, Isere	310	9.1
Germany, East	3356	12.2
Germany, Saarland	514	9.6
Iceland	89	10.9
Ireland, Southern	220	13.6
Italy, Florence	411	9.4
Italy, Genoa	360	9.7
The Netherlands	5013	11.2
Norway	2214	13.3
Poland, Warsaw	726	13.3.
Slovenia	766	10.5.
Sweden	4755	13.2
Spain, Basque County	481	7.7
Switzerland, Geneva	201	11.9
UK, England & Wales	15483	12.4
UK, Scotland	2844	13.3

	No. (all ages)	ASR
Oceania		
Australia, New South Wales	1654	8.4
New Zealand, non-Maori	1125	11.0
New Zealand, Maori	68	12.2
USA, Hawaii, White	122	14.2
USA, Hawaii, Hawaiian	36	8.3
USA, Hawaii Chinese	18	6.6
USA, Hawaii Japanese	95	8
Asia		
China, Shanghai	1321	5.8
China, Tianjin	535	5.3
Hong Kong	1164	7.4
India, *Bombay*	989	7.2
India, *Madras*	390	5.7
Israel: *All Jews*	1299	11.6
Israel*: born in America/Europe*	778	13.5
Israel: *born in Africa/Asia*	261	7.3
Israel: *non Jews*	37	3.0
Israel:*Jews born in Israel*	255	12.4
Japan, *Miyagi*	494	6.1
Japan, *Osaka*	1722	5.6
Korea, *Kangwha*	8	2.8
Kuwait: *Kuwaitis*	25	4.7
Philippines, *Manila*	692	9.4
Singapore: *Chinese*	585	10.7
Malay	80	9.9
Indian	28	7.5
Thailand, *Chiang Mai*	152	4.4
Vietnam, *Hanoi (1991-1993)*	82	2.9

from: Parkin et al (eds).
'Cancer Incidence in five countires'
vol VII, IARC Sci Publ no. 143, 1997

ASR = age-standardized rate

The incidence of ovarian cancer has remained stable over the last three decades in high risk developed countries, whereas in the underdeveloped countries the incidence has been reported to be increasing (Adami et al 1990, Parazzini et al 1991a). The documented increase could be due to improved medical care and reporting.

1.1.3 Incidence of Ovarian Cancer in Singapore

In Singapore, the cancer incidence in the females increased from 42% during the period 1968-72(n=5,099); 48.4% between 1988-92 (n=12,748) to 49.3% between 1993-7 (n= 15,679)(Table 1.1-2). The incidence of ovarian cancer saw a sharp rise from 222 cases in 1968-72 (Lee et al 1988) to 880 cases in 1993-97 (Chia et al 1996, 2000). It was the seventh most frequent cancers in females and from 1978-92 became sixth with incidence of 5.5% (1988-92) and 5.6% (1993-7) of all cancers in females. Breast cancer remains the most frequent cancer site with an incidence of 20.5% (1968-92) and 22.8% (1993-7) of all cancers in females (Chia et al 1996, 2000). The age-adjusted rate of incidence for ovarian cancer was 6.0/100,000 between 1968-72, 10.5/100,000 (1988-92) and rose to 11.4/100,000 (1993-7). Between 1988 and 1992 the highest incidence occurred in ethnic Chinese females (10.7) compared to Malay (9.9) and Indian women (7.5/100,000 per year)(Chia et al 1996). Ovarian cancer in Malays remain the most frequently diagnosed malignancy and is one of the few cancers which appears to have a higher risk than in Chinese (Chia et al 2000). The ovarian cancer incidence rate in Singapore falls between those of Western Europe and the rest of Asia. The incidence of this cancer showed a steady increase over time whilst stable or decreasing trends are observed in many developed countries. The age- and ethnic-adjusted relative risk for the period 1988 and 1992 was 1.7 times that

observed between 1968 and 1972 (Chia et al 1996). Cancer incidence and incidence of ovarian cancer in Singapore between 1968 and 1997 are shown in Tables 1.1-2 and 1.1-3. The frequency of ten most frequent cancers in females between 1988 and 1992 are shown in Fig 1.1-2 with age-specific incidence of ovarian cancer between 1993 and 1997 in Fig 1.1-3.

Table 1.1-2. Cancer Incidence in Singapore, 1968 - 1997.

Period	***Sex***	***Number***	***%***	***CR***	***ASR***
1968 - 72	*Male*	7,029	58.0	136.3	229.3
	Female	*5,099*	*42.0*	*103.7*	*154.5*
1973 - 77	*Male*	8,578	58.0	158.4	247.5
	Female	*6,204*	*42.0*	*119.2*	*161.6*
1978 - 82	*Male*	10,131	55.9	175.0	250.3
	Female	*8,004*	*44.1*	*142.8*	*176.0*
1983 - 87	*Male*	11,649	53.7	186.6	242.3
	Female	*10,026*	*46.3*	*165.2*	*182.9*
1988 - 92	*Male*	13,583	51.6	198.0	235.8
	Female	*12,748*	*48.4*	*190.7*	*191.8*
1993 – 97	*Male*	16,150	50.7	209.7	233.1
	Female	*15,679*	*49.3*	*208.8*	*198.1*

CR: Crude rate (per 100,000/year); ASR: Age-standardised rate (per 100,000/year)
from: Chia KS, Lee HP, Seow A and Shanmugaratnam K. ***Trends in cancer incidence in Singapore 1968/1992*** *and Cancer Incidence in Singapore 1993-1997. Published by Singapore Cancer Registry, 1996 and 2000.*

Table 1.1-3. Incidence of Ovarian Cancer in Singapore, 1968 – 1997.

Year	*No.*	*Age-standardised rate (per 100,000/year)*
1968 – 1972	222	6.0
1973 – 1977	263	6.3
1978 – 1982	411	8.6
1983 – 1987	497	8.8
1988 – 1992	702	10.5
1993 – 1997	880	11.4

Extracted from: ***'Trends in cancer incidence in Singapore 1968/1992 and Cancer Incidence in Singapore 1993- 1997*** *(Chia et al 1996, 2000)*

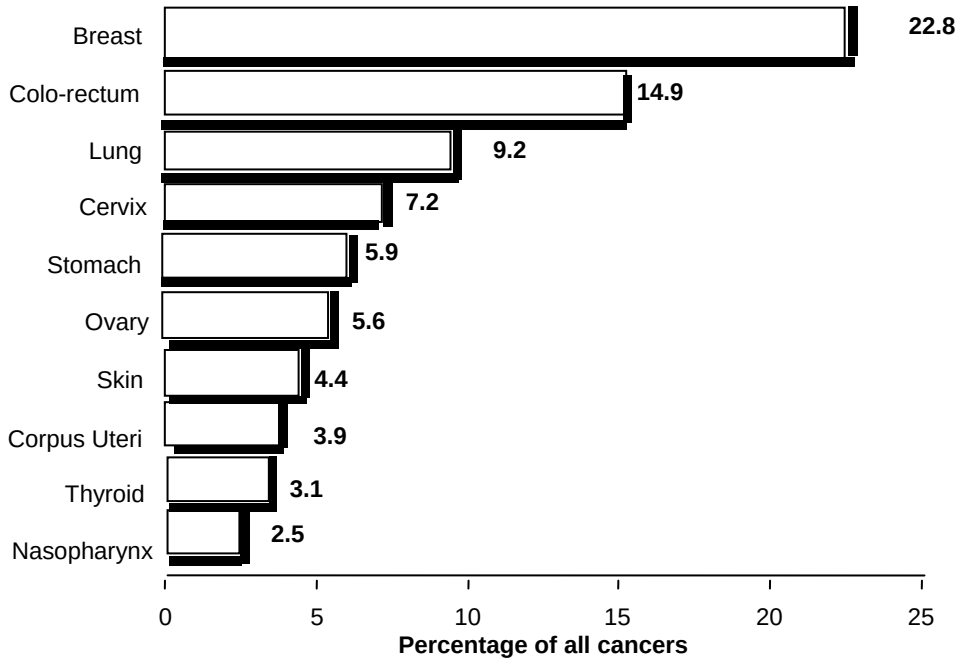


Fig.1.1-2. ***Ten most frequent cancers in females in Singapore, 1993-1997*** *(Chia et al 2000)*

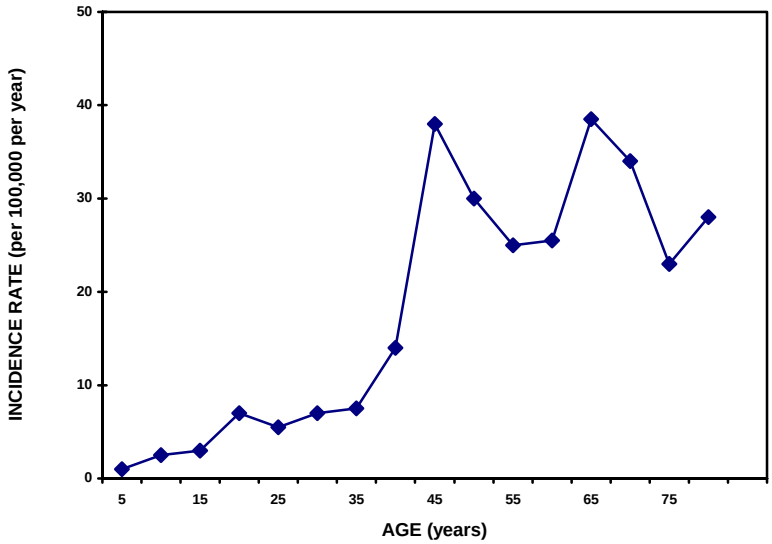


Fig 1.1-3. Age-specific incidence of ovarian cancer in Singapore, 1993-1997 *(Chia et al 2000).*

1.1.4 Histologic Type

Three main types of ovarian cancer have been identified as epithelial, germ cell and sex cord-stromal tumours, and age has influence on the pattern of these tumour incidences (Cramer et al 1981). The incidence of epithelial tumours increases with age and are more common in middle-aged women while germ cell tumours peaks in early postpubertal life and does occur constantly at older ages. The common epithelial ovarian cancer is derived from the 'surface epithelium' of the ovary and the tumour is not always homogenous as it consists of the presence of two or even three cell types, the neoplasm is classified on the basis of its predominant cellular element (Scully 1983). Germ cell tumours are frequent at younger ages of below 40 years (Koper et al 1996). The tumour is associated with nongestational ovarian choriocarcinoma and other germ-cell elements: dysgermonia, embryonal carcinoma or immature teratoma

(Piver 1983). Sex cord-stromal tumours increase in incidence with increasing age (Cramer et al 1981). The sex cord-stromal tumour is generally accepted to be made up of a group of cells in the developing gonads and includes all neoplasms which contain these various cellular elements alone, or in combination and in varying degrees of differentiation (Scully 1983). In children, ovarian cancers are usually germ cell tumours and are rarely of sex cord-stromal tumour type. Epithelial tumours occur after puberty and account for increasing numbers of ovarian cancers with increasing age. About 90-95% epithelial tumours are seen above the age of 35 years (Weiss et al 1977) and small variations of different subtypes are prevalent at different ages (Parkin et al 1988, Cramer et al 1981). Low malignant potential or borderline is characterized by good prognosis and may be analogous to *in situ* tumours of other organ sites.

1.1.5 Reproductive and Endocrine Factors

The risk of ovarian cancer is weakly associated to age at menarche and hardly to menopause, the risk decreases as the age at menarche increases. Nulliparity is an increased risk while lactation is protective (Harlap 1993). The risk of ovarian cancer increased with the number of ovulations in a woman's lifetime (Risch et al 1983; Whittemore et al 1989; Booth et al 1989;), a history of infertility or low parity (Joly et al 1974 ;McGowan et al 1979; Hildreth et al 1981, Booth et al 1989). Nasca et al (1984) found a higher risk in women who had tried to conceive but had failed. A strong correlation exist between family history of gynaecologic malignancy, either ovarian or endometrial and later development of ovarian cancer (McGowan et al 1979; Hildreth et al 1981). The odd ratio for positive family history is 18 times greater

than for patients with negative family history (Hildreth et al 1981). Late menopause, prolonged ovulatory age, increased number of spontaneous abortions and severe premenstrual symptomatology all have been related to risk factors (Joly et al 1974; McGowan et al 1979; Hildreth et al 1981). Others have associated ovarian cancer risk to hormone therapy for inducing ovulation in infertility (Shu et al 1989a; Dietl 1991). Since these drugs elevate gonadotrophin levels and cause superovulation, the reports on the association between the use of fertility drugs and ovarian cancer is conflicting (Bristow & Karlan 1996; Glud et al 1998).

1.1.6 Oral Contraceptives

Numerous case-control studies have shown that the risk of epithelial ovarian cancer is reduced by about 40% in women who have used oral contraceptives (Prentice & Thomas 1987) and about 50% in those who have used for five or more years (WHO 1989). Depending on the duration of use, the protective effect persists for ten or more years after discontinuation and is one of the strongest and most consistent features of the epidemiology of the disease (WHO 1989; Parazzini et al 1991). However, the pill gives no protection against non-epithelial tumours, at least in younger women (Casagrande et al 1983; Westhoff et al 1988; Shu et al 1989a,). The decline in the incidence of ovarian cancer and mortality in developed countries have been reported in several studies. This decline has been associated with the potential protective effects of oral contraceptives which were introduced in the 1960s and used worldwide (Adami et al 1990; Negri et al 1991; Coleman et al 1993; Ries 1993; Devesa et al 1995; Dos Santos et al 1995).

1.1.6-1 Other Contraceptives

Reports investigating into methods of birth control other than oral contraceptives have not shown any consistency in their relation to ovarian cancer. Diaphgrams and condoms, similarly with intra-uterine devices (IUCD) (Cramer 1982a, Booth et al 1989; Chen et al 1992), and vasectomies (Booth et al 1989) have not shown any significant relationship to ovarian cancer. Tubal sterilization and hysterectomy with oophorectomy have been associated with reduced risk (Mori et al 1984; Booth et al 1989; Koch et al 1988; Irwin et al 1991) while women with intact ovaries after hysterectomy have a lower-than-average risk of ovarian cancer. Hysterectomy and tubal sterilization are associated with protection for at least 20 years although it may wane thereafter (Irwin et al 1991; Miracle-McMahill et al 1997).

1.1.7 Postmenopausal Estrogen Therapy

Decreased risk in ovarian cancer could be associated with the use of exogenous estrogen, hormone replacement therapy (HRT) which reduces the high gonadotrophin levels of postmenopausal women. Few studies have shown such a reduction and a few with positive association (Ries et al 1998) while others have not observed such a relationship with HRT and ovarian cancer (Harlap 1993; Rodriguez et al 1997; Weiss et al 1982; Hempling et al 1997). The relative risk varies between 0.5 and 1.6 in eleven case-control studies (Annegers et al 1979; Hildreth et al 1981; La Vecchia et al 1982; Weiss et al 1982; Cramer et al 1983b; Tzonou et al 1984; Mori et al 1984; Harlow et al 1988; Wu et al 1988; Booth et al 1989; Hartge et al 1989). Enhanced risk were not seen in six studies (Hildreth et al 1981; Weiss et al 1982; La Vecchia et al 1982; Wu et al 1988; Hartge et al 1989; Booth et al 1989) one study suggested

enhanced risk for estrogen used for more than five years (Cramer et al 1983b). Rodriguez et al (1997) suggested that long-term use of estrogen replacement therapy might increase the risk of fatal ovarian cancer. An association of ovarian cancer has also been suggested with the use of stilbestrol (Hoover et al 1977).

1.1.8 Talc

Asbestos is an accepted cause of mesothelioma (Selikoff et al 1965) and was a contaminant in talcum powder prior to the mid- 1970s (Hildick-Smith 1976). Ovarian cancer is more common in women with asbestosis (Newhouse et a 1972) and occupational exposure to talc has been associated with lung disease but there is a controversy whether talc induces disease in humans (Hildick-Smith 1976). Enhanced risk of ovarian cancer has been associated with the use of talc on the perineum (Cramer et al 1982b; Whittemore et al 1988; Chen et al 1992) and is influenced by dose response effect, duration of use or with frequency of use. In contrast, talc used on diaphragms and condoms is not associated with increased ovarian cancer risk (Cramer et al 1982b; Hartge et al 1983; Cook et al 1997).

1.1.8-1 Dietary Factors

Excessive dietary intake of animal fat or red meat has been reported to enhance the risk of epithelial ovarian cancer (Byers et al 1983; La Vecchia et al 1987; Shu et al 1989). Similarly protective roles have been suggested for dietary fish, vegetables and carbohydrates (La Vecchia et al 1987; Shu et al 1989b). These associations are found to be weak and there are too few studies to draw any firm conclusions (Harlap 1993). Cramer and his co-workers (1989) proposed that an increased risk of epithelial ovarian cancer might be seen in populations that consume a high fat-galactose diet but

lack the enzyme galactose-1-phosphate uridyltransferase to break down the galactose to glucose, thus exposing the ovary to long periods of high galactose concentration.

Alcohol drinking has been suggested to be protective against ovarian cancer especially in young women (Byers et al 1983). However, the large population-based CASH study (Gwinn et al 1986) found no such effects of alcohol, similarly for smoking in preventing ovarian cancer (Byers et al 1983; Tzonou et al 1984; Franks et al 1987).

1.1.8-2 Mumps and Other Infectious Diseases

The association between past history of mumps and ovarian cancer have been reported by others (Menczer et al 1979; McGowan et al 1979; Cramer et al 1983a; Tzonou et al 1984; Cramer 1985; Shu et al 1989a; Chen et al 1992). The association of rubella, measles, influenza/pneumonia and shingles have also been reported (Wynder et al 1969; Risch et al 1983; Lesher et al 1985; Gwinn et al 1990). These highly speculative reports on the association between viral infections, including mumps and increased risk of ovarian cancer have been conflicting. Menczer and his group in Israel (1979) demonstrated low mumps antibody in women with ovarian cancer including patients after chemotherapy whilst another group in China (Chen et al 1992) reported high antibody titres when compared with controls.

1.1.8-3 Blood Group

Carcinoma of the ovary was reported to be associated with ABO blood group system. Osborne and DiGeorge (1963) selected neoplastic disease of the ovary for this association study, and concluded that ovarian neoplasms that was associated with blood group A have a glandular type of epithelium and those from other blood groups

are solid rather than cystic. Bjorkholm (1984) also reported an increased association of ovarian cancer in women with blood group A.

1.1.8-4 Inflammation

It has been suggested that other additional mechanism that may underlie ovarian cancer is inflammation. Concomitant rapid DNA turnover and defective repair, oxidative stress and raised bioactive substances may contribute to this disease. Inflammation of both the epithelium and follicle are associated with incessant ovulation and local pelvic inflammation may also increase risk. However, further data is required to confirm the hypothesis that inflammation is a central biologic process in ovarian cancer risk (Ness & Cottreau 1999).

1.1.9 Hereditary Factors

The aetiology of ovarian cancer is unknown but hereditary disorders of ovarian neoplasms have been extensively reviewed (Lynch and Kullander 1987) and is thought to account for 5% to 10% of all ovarian cancers. Familial ovarian cancer is not a rare occurrence and is associated with two conditions; site-specific, the most common form which is restricted to the ovarian cancer and the breast/ovarian cancer syndrome with clustering of ovarian and breast cancer cases in extended pedigrees (Lynch et al 1978). Familial ovarian cancer showed significantly lower age onset than in the general population (Lynch et al 1993, Goldberg et al 1997). Ovarian cancer is strongly associated with other cancers within families especially in ovarian (Hildreth et al 1981; Cramer et al 1983b; Tzonou et al 1984), prostate (Cramer et al 1983c; Koch et al 1988), breast (McGowan et al 1979; Hildreth et al 1981; Koch et al 1988; Schildkraut et al 1988; Thompson and Schildkraut 1991; Parazzini et al 1992),

colorectal (Tzonou et al 1984; Schildkraut et al 1988; Goldgar et al 1994), lung and other reproductive cancers in first-degree relatives of either sex (McGowan et al 1979; Cramer et al 1983b; Mori et al 1984; Schildkraut et al 1988), For women who have a first-degree relative with ovarian cancer may have as high as 50% chance of developing this familial disease compared to a 1.4% (1 in 70) chance for women without a family history. Those with breast cancer, relative estimates have varied from 0.6 to 6.1 (Hildreth et al 1981, Cramer et al 1983c; Koch et al 1988); mostly above one. A family history of endometrial cancer probably might not raise the risk of ovarian cancer (Schildkraut et al 1989) although it did in some studies (Hildreth et al 1981; Tzonou et al 1984). The genetics of ovarian carcinoma is not well documented. Cytogenetic investigations revealed alterations in chromosomes 1, 3, 6 and 11 which are frequently associated with ovarian cancer (Atkin and Pickthall 1977; Wake et al 1980; Whang-Peng et al 1984).

A candidate gene for *BRCA1* was identified by positional cloning in 1994 (Miki et al) and confirmed by mutation analysis in high-risk breast cancer families (Castilla et al 1994; Futreal et al 1994; Friedman et al 1994). *BRCA1* gene was isolated since it was first mapped to chromosome arm 17q in 1990 by linkage analysis (Hall et al 1990; Narod et al 1991). A second breast cancer susceptible gene, *BRCA2*, was localised through linkage studies to the long arm of chromosome 13 and cloned (Wooster et al 1994). It accounts for 35% of hereditary breast cancer and is also associated with male breast cancer, ovarian, prostate and pancreatic cancers (Wooster et al 1994; Gayther et al 1995). These genes together account for about 75% of strong family history for breast and ovarian cancers. *BRCA1* accounts for approximately 45% of families with significantly high breast cancer incidence and at

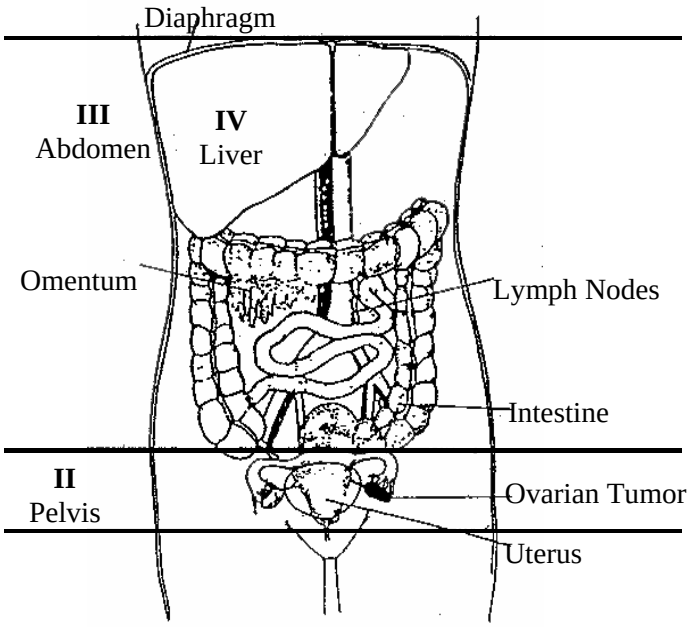
least 80% of families with increased incidence of both early-onset breast cancer and ovarian cancer (Easton et al 1993 a,b; Simard et al 1994). *BRCA2* mutation carriers have a life time risk of breast cancer of about 85% but their risk for ovarian cancer is lower (10%-20%) (Easton et al 1993b, 1995). Males carrying the mutated *BRCA1* gene has a three-fold increased risk of prostate cancer, and males and females at a four-fold increased risk of colon cancer (Ford et al 1994). More than 100 mutations in the gene have been described, many of which result in premature truncation of protein transcription (Miki et al 1994). Although *BRCA1* has been identified, more genes involved in gynaecologic malignancies remain to be discussed, and the clinical significance of the cancer gene already known is still in its infancy (Lynch et al 1998).

The International Federation of Gynecology and Obstetrics (FIGO) staging of primary carcinoma of the ovary and the 4-stages of ovarian cancer (stages I to IV) (Piver et al 1997) are shown in Table 1.1-4 and Fig. 1.1-4.

1.1.10. Table 1.1-4. FIGO Staging of primary carcinoma of the ovary.

FIGO Stage		Tumor Characteristics
I		**Growth limited to the ovaries**
	IA	Growth limited to one ovary; no ascites; no tumor on the external surface; capsule intact
	IB	Growth limited to both ovaries; no ascites; no tumor on the external surfaces; capsule intact
	IC	Tumor either stage IA or IB but with tumor on surface on one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells; or with positive peritoneal washings
II		**Growth involves one or both ovaries with pelvic extension**
	IIA	Extension or metastases to the uterus or tubes
	IIB	Extension to other pelvic tissues
	IIC	Tumor either stage IIA or IIB, but with tumor on surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells; or with positive peritoneal washings
III		**Tumor involves one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals stage III. Tumor is limited to the true pelvis but with histologically proven malignant extension to small bowel or omentum**
	IIIA	Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
	IIIB	Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes are negative
	IIIC	Abdominal implants greater than 2 cm in diameter or positive retroperitoneal or inguinal nodes
IV		**Growth involves one or both ovaries, with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to stage IV. Parenchymal liver metastasis equals stage IV.**

International Federation of Gynecology and Obstetrics (FIGO) 1987.



The 4 Stages of Ovarian Cancer

I Confined to Ovary
II Spread Outside of Ovary Confined to Pelvis
III Spread to Abdomen
IV Spread to Liver or Beyond Abdomen

Fig 1.1-4. ***The four stages of Ovarian Cancer*** (Piver and Wild 1997).

1.1.11 MORTALITY TRENDS IN OVARIAN CANCER

It is important to know the limits and uncertainties of cancer death certification and their trends over time particularly for the elderly, and there is no widespread nor generalised upward trend in cancer mortality except in lung and other tobacco-related neoplasms. Generally, cancer mortality trends over the last four decades have been favourable for elderly women (Levi et al 1996)

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Five-year survival rates for patients with epithelial ovarian cancer remain fairly static at between 30 to 40%, despite the use of aggressive treatment regimens including, cytoreductive surgery; multi-agent chemotherapy regimens; salvage therapies (Silverberg et al 1990, Miller et al 1993). The lack of progress may be usually attributed to the advanced stage of the disease at the time of diagnosis and improvement in survival rates may occur when screening methods are developed to screen populations at high risk for ovarian cancer.

The distribution of cancer of the ovary is similar to that reported for breast cancer with high incidence in the United Kingdom and Ireland. In Europe, concentrations of high-risk regions were seen with Denmark having the highest incidence (11.2) and above-average rate in Germany. A clear North-South gradient incidence rate is seen in Europe with lowest rates in much of France and Italy. In the United States, Japan and Australia, ovarian cancer accounts for 6.0%, 2.9% and 6.0% respectively of all cancer deaths in females (Smans et al (eds) 1992).

Between 1983 - 1987, the highest mortality rates per 100,000 women for ovarian cancer in central Europe were found in Czechlovaskia (8.52), East Germany (8.24), Austria (8.23) with median mortality rates in West Germany (7.84), Hungary (7.22) and Poland (6.44), Bulgaria (4.94), Romania (4.63) and the lowest rate in

Yugoslavia (4.35). The highest ovarian cancer mortality worldwide were found in Denmark (10) and the lowest in Japan and south of Europe (about 3). The lowest incidence rates (<4) were found in African and Asian registries as well as in native Kuwaitis. The incidence in central Europe ranged from 5.6 (Szaboles, Hungary) to 13.6 (Bohemia and Moravia, Czechlovaski) (Zatonski et al 1996).

Epithelial ovarian cancer is associated with the highest mortality rate of all gynaecologic malignancies. No symptoms or signs are manifested in the early stages of the disease. The prognosis of the disease is generally poor as reflected by the lower than 30% five-year survival rate (Office of Pop. Cons. & Surveys 1993 [England & Wales]) and between 30% to 40% (Silverberg et al 1990). The poor prognosis of the disease is mainly due to the advanced stage of the disease (Stage III and IV) diagnosed in more than 75% of cases of ovarian cancer despite advances in surgery and chemotherapy (Miller et al 1993). The prognosis of patients with mucinous tumour is more favourable than in patients with serous tumours, and patients with clear cell tumours was worse (Bjorge et al 1998b; Tammela et al 1998).

Ovarian cancer mortality among the elderly in developed countries is rising, with increasing age-dependency (Levi et al 1996; Koper et al 1996) whereas mortality in the younger-age group is declining (Koper et al 1996). The certified mortality rates from ovarian cancer in women aged between 65 and 84 years were between 30 and 50/100,000 in most northern European and American countries, Australia and New Zealand. Lower mortality rates in eastern Europe and Japan in the 1950s and 1960s were seen with appreciable rise in the early 1990s which remained generally lower than reported for North America or Europe (Levi et al 1996). In the Netherlands, the mortality rates declined from 13.1/100,000 (1969-1973) to 11.4/100,000 between

1989-1993 (Koper et al 1996). In the United States, it was estimated that 26,600 women will be diagnosed with ovarian cancer in 1995 and 14,500 will die from the disease (American Cancer Society 1995; T-Luna & Mitchell 1995). The overall ovarian cancer mortality rates had changed little in the United States prior to 1979. However, the increasing mortality rates between the period 1979 to 1995 reflects a growing aging population, where increase mortality rates were observed in older women above 65 years and decreasing mortality in younger women (Oriel et al 1999). The overall mortality rates in the United States for the period between 1979 and 1995 were; Whites (deaths 185,976, rate 9.9/100,000 women); Blacks (deaths 15,319, rate 8.1/100,000) and others (death 2224, rate 4.9) (Oriel et al 1999).

In England and Wales, the age-standardized death rate rose from 11.8 to 14.2/100,000 between 1950 and 1991. There is a clear divergence in trend between the younger and older age group in mortality rates. The death rate trend fluctuated at around a mean of 0.8/100,000 in the 15-34 age group between 1950 and 1970 and a downward trend from 0.9 (1970) to 0.5/100,000 in 1991. Similar trend was seen in the 35-54 year age group with a stable mean of 13.5/100,000 between 1950 and 1970 but thereafter declined to 9.7/100,000 in 1991. No decline in mortality was observed in women above 55 years who experience an increase from 29-35/100,000. The mortality rate in the older age group of over 65 years showed an increase from 31 to 48/100,000 between 1950 and 1991 (Mant and Vessey 1995).

At the National Taiwan University Hospital between 1980 -1989, the observed 5-year survival rate was 29.4% for epithelial ovarian cancer, 51.4% for non-epithelial and 64.5% for germ-cell tumours (Chen et al 1994). There is no homogeneous trend in the international mortality rates for ovarian cancer (Coleman et al 1993). Japan and

Italy showed a rise in mortality between 1955-1985 whilst in Australia and The Netherlands, no sustained rise was seen, similarly in Norway. The mortality rate in the United States and Canada has fallen over this period. Most countries showed a rising mortality trend in 55-84 age group except Denmark where the mortality rates has been falling since 1970. Survival rates have increased since the introduction of more aggressive treatment modalities in the mid-1970s with extensive surgery followed by platinum-based chemotherapy regimens. Short-term survival rate for epithelial ovarian cancer has improved but no major improvement in the 5-year survival rate were seen (Ries 1993; Balvert-Locht et al 1991; Averette et al 1995; Bjorge et al 1998a).

In Thailand, granulosa cell tumour of the ovary accounted for 5.8% in 620 ovarian malignancies during the period of study, 1984 to 1994. It showed a 5-year survival of 94% in early stages and 25% in advanced stages with an overall 62% for all stages of the disease (Maleemonkol et al 1996). The mortality rate from this tumour is generally low (11-22%) but it displayed a higher malignant potential in Thailand.

The age-standardized ovarian cancer mortality in the elderly between 1955 and 1992 (Levi et al 1996) is shown in Table 1.1-5. The mortality trends between 1955 and 1985 in selected countries (Mant and Vessey 1995), the Netherlands between 1954 and 1993 (Koper et al 1996) and the 5-year survival rate of ovarian cancer in Norway between 1975 and 1994 (Bjorge et al 1998b) are shown in Figures 1.1-5 to 1.1-7.

Table 1.1-5. Age-standardized (65-84 years, world standard) death certification rates per 100,000 women from ovarian cancer in various countries, 1955 – 1992 (Levi et al 1996).

Country	*1955-1959*	*1990-1992*	*% Increase*	*Country*	*1955-1959*	*1990-1992*	*% Increase*
Austria	47.4	49.2	3.9	Spain	1.8 1	8.4	920.6
Belgium	21.2	44.7	110.9	Sweden	39.2	44.5	13.6
Czechoslovakia	24.4	31.6	29.7	Switzerland	40.0	48.0	20.0
Denmark	49.7	59.2	19.3	UK, *England/Wales*	33.9	49.1	44.6
Finland	26.0	37.1	42.8	UK, *Scotland*	30.1	55.8	85.7
France	12.9	36.6	182.7	Canada	35.2	37.0	4.9
Germany	36.1	45.8	26.7	U.S.A.	33.5	41.2	22.9
Greece	2.9*	15.7	435.0	Japan	3.2	14.5	358.2
Ireland	14.1	48.9	246.2	Australia	28.2	36.2	28.6
Italy	10.2	24.4	140.0	New Zealand	34.1	44.9	31.9
The Netherlands	35.3	53.1	50.3				
Norway	32.4	44.5	37.3	*(* rates for 1965-1969 only available)*			

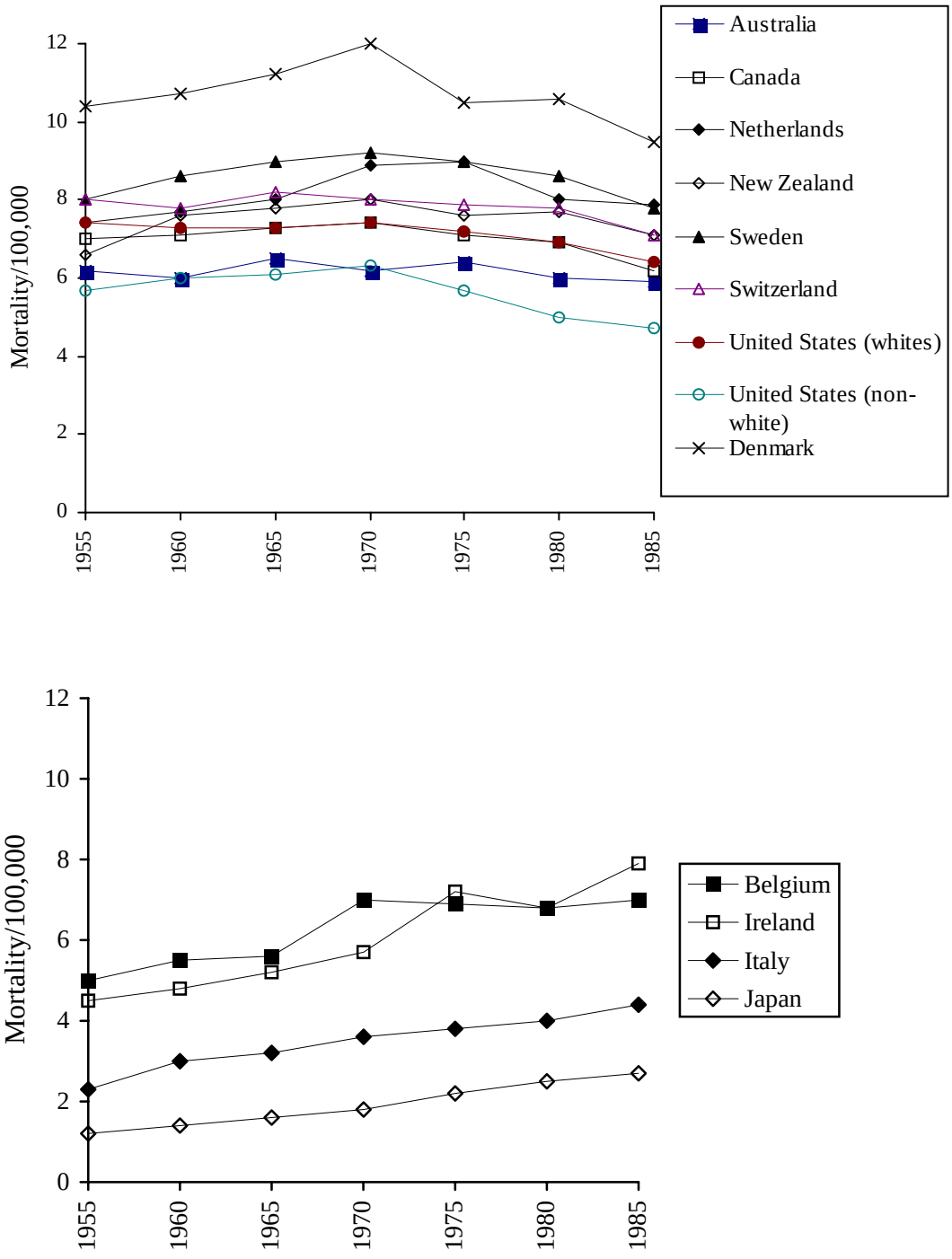

Fig.1.1-5. *Mortality from ovarian cancer in international selected countries, 1953-1987 (upper fig.). Countries that did not show a rise in mortality and (lower fig.) countries that did show a rise. (Mant and Vessey 1995)*

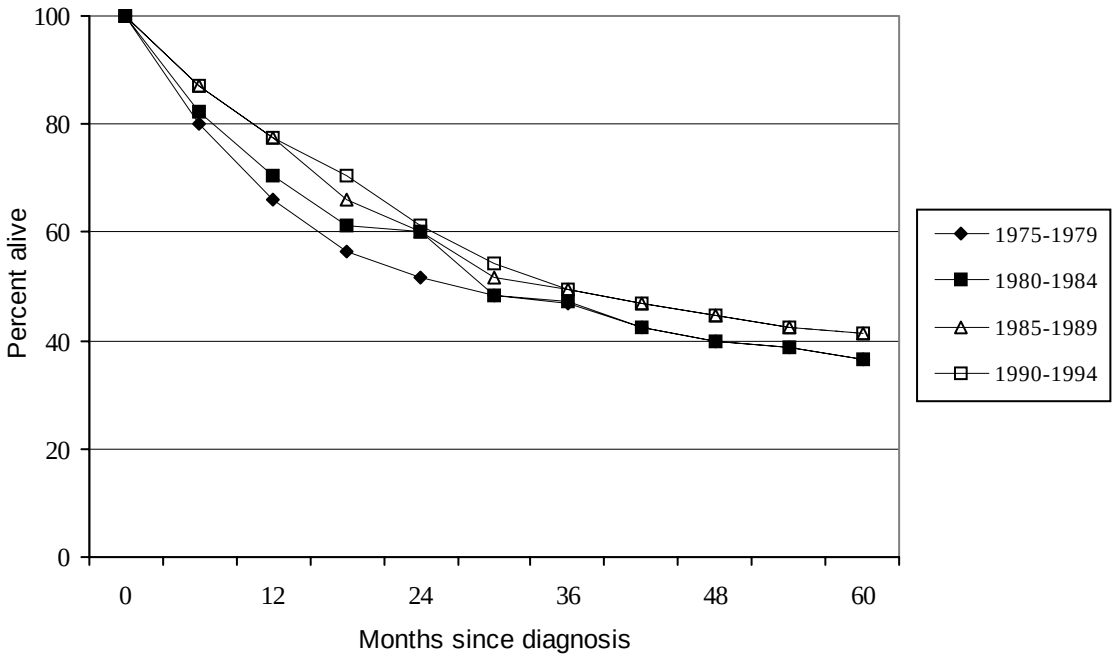

Fig. 1.1-6. *Five-year survival of patients with epithelial ovarian cancer in Norway, 1975 - 1994, adjusted for age (Bjorge et al 1998).*

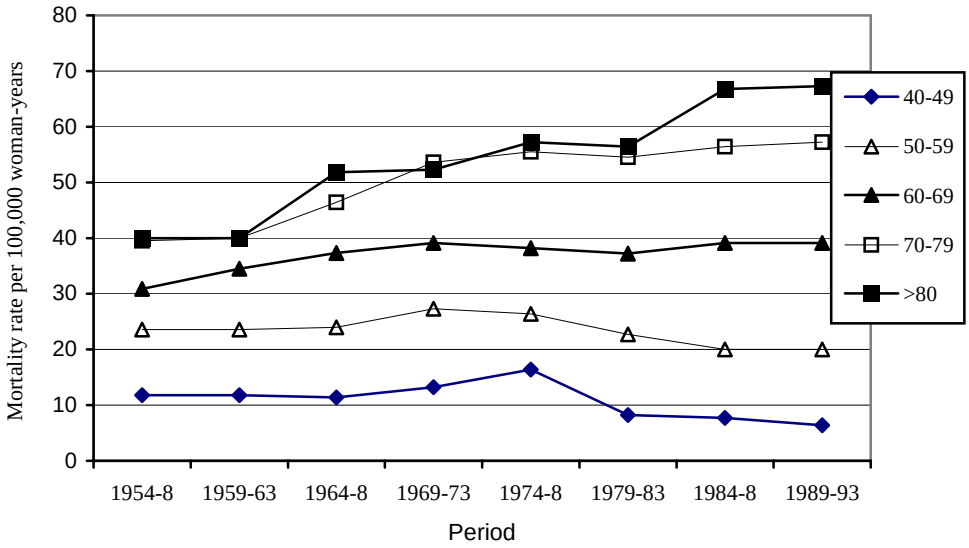

Fig. 1.1-7. *Age-specific ovarian cancer mortality in the Netherlands, 1954-1993* (*Koper et al 1996*).

1.1.12 Mortality Trends of Cancer in Singapore

In Singapore, the comprehensive population-based registry only began in 1968, primarily to obtain information on cancer patterns in Singapore. The known published mortality rate for ovarian cancer in Singapore for 1965 was 5.0/100,000 per year (10 deaths), and in 1985 it was 7.4/100,000 per year (26 deaths) in the 30 to 74 year age group (Coleman et al 1993). This coincides with increasing incidence of ovarian cancers recorded between 1968 and 1997 (Table 1.1-3).

Mortality in cancer patients continued to increase in importance over the last decade. Of the 75,871 deaths in 1993-1997, malignant neoplasms accounted for 19,408 cases. Mortality from cancer was 25.6% (1993-7) compared with 14.8% in 1968-1972. Lung cancer had the highest incidence among all cancers in males and females and followed by liver cancer in males and breast cancer in the females (Chia et al 2000).