REVIEW

Risk Factors for Ovarian Cancers: Do Subtypes Require Separate Treatment in Epidemiological Studies?

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Abstract

Epidemiological studies of cancer of the ovaries , among the leading sites for cancer incidence and mortality in women in very many countries of the world, have pointed to high saturated fat and carbohydrate intake, postmenopausal hormone replacement therapy and use of cosmetic talc as risk factors. Conversely, vegetable consumption, parity, lactation and generally appear to confer protection. Genetic influence also clearly plays a role, women with mutations in the BRCA1 or BRCA2 genes having an elevated risk, for example. Overall there appear to be shared risk factors for breast cancer. However, there are many types of epithelial ovarian cancer and cross-country comparisons of incidence data from various cancer registries in Europe and North America published in the IARC Cancer Incidence in Five Continents Vol VII suggest that only the serous type is linked to mammary tumour development. Thus future studies should concentrate more attention on the individual subtypes of ovarian cancer in order to better establish preventive measures.

Key words: Ovarian cancer - subtypes - adenocarcinomas - risk factors - pathophysiological epidemiology

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Prevalence

Incidence and Mortality

Cancer of the ovary is of major importance in the developed world and even in developing countries it ranks high on the list of cancers causing mortality in females. In the US it is among the five leading sites for incidence and mortality in women. Within the Asian Pacific, there is a great range but in all countries the figure is appreciable and a rise can be expected with adoption of a western lifestyle (see Table 1).

Histopathology

The most common type is epithelial, originating from the surface germinal epithelium of the ovary. Since the coelemic epithelium can differentiate into serous, ciliated columnar cells, or mucous non-ciliated cells, epithelial tumours may have various forms, the most common being serous, mucinous, endometrioid, clear cell and non-specific adenocarcinoma. Borderline lesions have low malignant potential and may be analogous to in situ tumours of other organs, stage I lesions having 5-year survival rates of approximately 90%. In contrast, stage III cancers have a very poor prognosis. More than 75% of cases are diagnosed with advanced disease.

Risk Factors

Hormonal

Some studies of ovarian cancer have revealed a slightly increased relative risk with early age at menarche (Parazzini et al., 1989; Franceschi et al., 1991a; Parazzini et al., 1991; Risch 1998) and late menopause may elevate the risk (Parazzini et al., 1989; Franceschi et al., 1991a; Parazzini et al., 1991), although not all data are in agreement (Adami et al., 1994). A role for ovulation also indicated by reduced risk in those with irregular menstrual cycles (Parazzini et al., 1991). Nulliparity and low parity also associated with

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Table 1. Age-adjusted Incidence Rates for Ovarian Cancer in Selected Countries of the Asian Pacific

Country and Group	Rate/100,000	Percentage of all female cancers
US, Hawaii, White	14.2	4.8
Israel, All Jews	11.6	4.9
Singapore, Malay	9.9	7.4
Philippines, Manila	9.4	4.8
Australian Capital Territory	8.1	3.5
China, Hong Kong	7.4	3.5
China, Shanghai	5.8	3.8
India, Madras	5.7	4.4
Japan, Osaka	5.6	3.6
Thailand, Khon Kaen	4.4	3.4
Viet Nam, Hanoi	2.9	3.3

Data from Cancer Incidence in Five Continents, 1997

elevated risk in most studies (Franceschi et al., 1991a; Parazzini et al., 1991; Risch et al., 1994) while each birth may confer a 10-16% reduction in risk (Hartge et al., 1994; Hankinson et al., 1995; Adami et al., 1994). Effects diminish with time (Adami et al., 1994; Albrektsew et al., 1996). Incomplete pregancies may also confer protection (Tzonou et al., 1984; Kvale et al., 1988; Mori et al., 1988) although this is not always the case (Wu et al., 1988; Hartge et al., 1989). Oral contraceptives generally protective, this correlating with the period of use (Franceschi et al., 1991b; Whittemore et al.,1992; Gross and Sclesselman JJ, 1994; Risch et al., 1994; Vessey and Painter, 1995; Beral et al., 1999; IARC, 1999; La Vecchia and Franceschi, 1999; Chiaffarino et al., 2001). Similar effects among parous and non-parous (Hankinson et al., 1995). However, hormone replacement therapy after menopause may be associated with a moderate excess (Rodriguez et al., 1995; IARC, 1999; Negri et al., 1999; Coughlin et al., 2000) but this is not always the case (Weiss and Hill, 1996; Hempling et al., 1997). Increase in the level of luteinizing hormone due to polycystic ovarian syndrome may elevate risk of ovarian cancer, especially in women who are very lean at age 18 (Schildkraut et al., 1996).OCs may act by suppressing production of androgens, elevated serum androstenedione and dehydroepiandrosterone being risk factors (Helzlsour et al.,1995). Need to measure in ovary itself rather than the serum?. Endometriosis, which is associated with hormonal abnormalities also predisposes to certain types of ovarian cancer (Brinton et al., 1997) although in this case the backgtround inflammatory changes could be playing a role ?. Numbers of ovulatory cycles are positively correlated with risk (Bernal et al., 1995; Schildkraut et al., 1997).

Infertility and Fertility Drug Use

Ovulation induction with hormones and ovarian cancer are associated but this is not necessarily causal since infertility alone is an independent risk factor (Bristow and Karlan, 1996; Chen et al., 1992). Multiple stimulation was found to be significant in one study (Grimizis et al., 1995) and "incessant ovulation" as a predisposing condition was stressed by Casagrande et al (1979) following the suggestion of Fathalla (1972). Increase with use of fertility drugs has been repeatedly documented (Harris et al.,1992; Rossing et al., 1994). Pelvic inflammatory disease, one cause of infertility may stimulate proliferation in the surface epithelium and increase risk (Risch and Howe, 1995).

Lactation

Breast-feeding confers a lower risk of ovarian cancer (Gwinn et al., 1990), perhaps by suppressing ovulation, the effect being strongest in the months immediately after delivery (Whittemore et al., 1988). Inverse association also reported for longer average period of lactation per pregnancy (Risch et al., 1994).

Tubal Ligation and Hysterectomy

A number of case-control or hospital record studies have demonstrated protection against ovarian cancer development with tubal ligation (Hankinsson et al.1993; Rosenblatt and Thomas, 1996; Green et al., 1997; Kreiger et al., 1997; Miracle-McMahill HL et al ., 1997). This may be by blocking access to irritable contaminants like talc (Green et al., 1997) but the fact of particularly strong influence on clear cell and endometrioid tumors suggests that mechanism could be hormonal (Rosenblatt and Thomas, 1996). In India, a low risk country because of the multiparity and early childbirth, this type of surgery if frequent and significantly reduces risk, with an odds ration of 0.25 in one study (Nandakumar et al., 1995). Hysterectomy also may exert beneficial influence (Risch et al., 1994), but one report suggested that this is not effective after ligation (Whittemore et al., 1988). Whether there are growth fctors secreted by the uterus which could have an impact has been suggested but unclear (Cramer and Xu, 1995).Hyperplasia and metaplasia of the ovarian surface epithelium in women with endometrial carcinomas also suggests a hormonal influence on ovarian carcinogenesis (Resta et al., 1987).

Talc and Exogenous Agents

Cosmetic talc use around the perineum is a possible risk factor for ovarian cancer (Harlow et al., 1992), although the data are not conclusive (Cook et al., 1997). If talc is contaminated with asbestos (Cramer et al., 1982) this could have an impact since asbestos workers have an elevated risk (Heller et al., 1996). Asbestos fibers can find their way to the ovaries as can talc (Wehner, 1994). No link with smoking (Whittemore et al., 1988; Engeland et al., 1996). Employment as a hairdresser (Boffetta et al., 1994) use of antidepressants (Harlow and Cramer, 1995). NSAIDs or analgesics, aspirin and paracetamol, reduce risk (Cramer et al., 1998).

Energy and Diet

No consistent effects were noted in case-control studies of lactose intake (Risch et al., 1994; Herrington et al., 1995) or Brassica vegetable consumption (Verhoeven et al., 1996).

However, tall stature, reflecting weight gain in early years of life (Barker et al., 1995) and BMI associated with elevated risk (Purdie et al., 1995). With regard to ovarian neoplasia, a sedentary existence has been reported to increase the likelihood of tumor development (Dosemeci et al, 1993; Zheng et al, 1993). However, in one cohort study of post-menopausal women, an incremental elevation in the relative risk of ovarian cancers was noted in moderate and high exercisers (Mink et al, 1996).Increased body weight is a risk factor (Mori et al., 1996, Purdie et al., 1995), as is a high dietary intake (Tomao et al., 1992). However, there does not appear to be any link to NIDDM (Adler et al., 1996) and serum levels of DHEA have been found to be increased in ovarian cancer patients (Helzlsouer et al., 1995)

Genetic Factors

Clinically, it has long been known that familial clustering may occur for ovarian cancers (Piver et al., 1984) with links to breast, colon and endometrium (Lynch et al., 1981). Supported by epidemiological case-control studies (Schildkraut and Thompson, 1988). Three main syndormes associated with ovarian cancer (Bewtra et al., 1992), The hereditary pattern is suggestive of an autosomal dominace with variable penetrance (Eby et al., 1994). In terms of individual genes, there is close linkage with the breast cancer susceptibility genes (BRCA1 and BRCA2). Families with BRCA1 and BRCA2 mutations represent two separate syndromes of site-specific familial ovarian cancer and hereditary breast/ovarian cancer (Boyd et al., 1997) and furthermore there are those individuals who have ovarian cancer as part of the hereditary nonpolyposis colorectal cancer (HNPCC) syndrome (Lynch II syndrome) due to mutations in DNA mismatch repair genes such as MSH2, MLH1, PMS1, and PMS2 (Lynch et al., 1996).

BRCA1 and BRCA2 mutations are most likely occur in patients with familial ovarian cancer (Szabo et al., 1997). Ford, et al., (Ford et al., 1995) estimate the frequency of BRCA1 mutations in the general population to be 0.06% and BRCA1 mutations are responsible for 5.7% of ovarian cancers under the age of 40, 4.6% between the age of 40 and 50, and 1.1% above age 50. Furthermore, individuals from high-risk families with BRCA1 mutations have an up to 87% cumulative risk of breast cancer by age 70, in addition to a four-fold increased risk for colon cancer and a three-fold increased risk for prostate cancer (Ford et al., 1994). The reported risk for ovarian cancer and breast cancer in BRCA2 mutation carriers is 27% and 84%, respectively (Ford et al., 1998).

Management guidelines of prophylactic oophorectomy have been put forth by the American Society of Clinical Oncology and by the Cancer Genetics studies Consortium (Statement of the American Society of Clinical Oncology., 1996; Burke et al., 1997), under the individualization based on her age, reproductive desires, and the calculated extent of risk based on a thorough pedigree analysis and genetic testing results. The performance of a prophylactic oophorectomy will reduce but not eliminate the risk for the development of primary peritoneal cancer even after this operation with a reported frequency of about 2% to 10% (Tobacman et al., 1982; Piver et al., 1993).

Cancer Registry Comparisons

Mucinous lesions do not appear to share the same risk factors as the other types of epithelial tumours of the ovary (Risch et al., 1996).However, data on this question are limited. To cast light on associations between different subtypes the ecological approach may be of interest. Organ incidence data and percentage distributions of microscopically verified cases for ovarian tumor subtypes (serous/mucinous/endometrioid/clear/non-specific adenocarcinoma) were therefore accessed from the IARC/WHO Cancer Incidence in Five Continents (Vol. VII) (Parkin et al., 1997). The countries/registries investigated in North America were Canada (Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland, Northwest Territories, Nova Scotia, Ontario, Prince Edward island, Quebec, Saskatchewan, Yukon), Central California (Whites and Hispanics), Los Angeles (Whites, Hispanics, Blacks, Chinese, Filipinos, Koreans and Japanese), San Francisco (Whites, Hispanics, Blacks, Chinese, Filipinos and Japanese), Connecticut (Whites and Blacks), Atlanta (Whites and Blacks), Iowa, New Orleans (Whites and Blacks), St Louis (Whites and Blacks), Detroit (Whites and Blacks), New Mexico (Whites and Hispanics), Utah, Seattle and Hawaii (Whites, Chinese, Filipinos, Hawaiians and Japanese). In Europe they were the UK (England and Wales, Yorkshire, Mersey, Scotland, South Thames, South Western, West Scotland,Yorkshire), France (Bas-Rhin, Calvados, Doubs, Haut-Rhin, Herault, Isere, Somme, Tarn), Italy (Ferrara, Florence, Genoa, Latina, Macerata, Modena, Parma, ragusa, Romagna, Torino, Trieste, Varese, Veneto), Spain (Asturias, Basque Country, Granada, Mallorca, Murcia, Navarra, Tarragona, Zaragoza), Iceland, Southern Ireland, the Netherlands, Denmark, Norway, Sweden, Finland, the Länder of the former East Germany, Austria (Tyrol) , Switzerland (Basle, Geneva, Graubunden, Neuchatel, St Gall-Appenzell, Valais, Vaud, Zurich), Estonia, Poland (Cracow, Kielce, Lower Silesia, Warsaw), the Czech Republic, Slovakia, Slovenia, and former Yugoslavia (Vojvodina). The significance of correlations was assessed with the JMP statistical package, version 3.1 (SAS Institute, Cary, NC) on a Macintosh computer. Simple and partial correlation co-efficients were both generated, the results for significance between pairs of cancers being summarized in Table 2. Significant cross-registry correlations were noted for many cancers, but most of these did not persist on partial analysis.

Ovary-Breast

Data for total ovary and breast cancers and their correlations for the American and European registries are illustrated in Figure 1. A number of general points are clear from the graphs. In the US (Fig 1a) the whites have higher

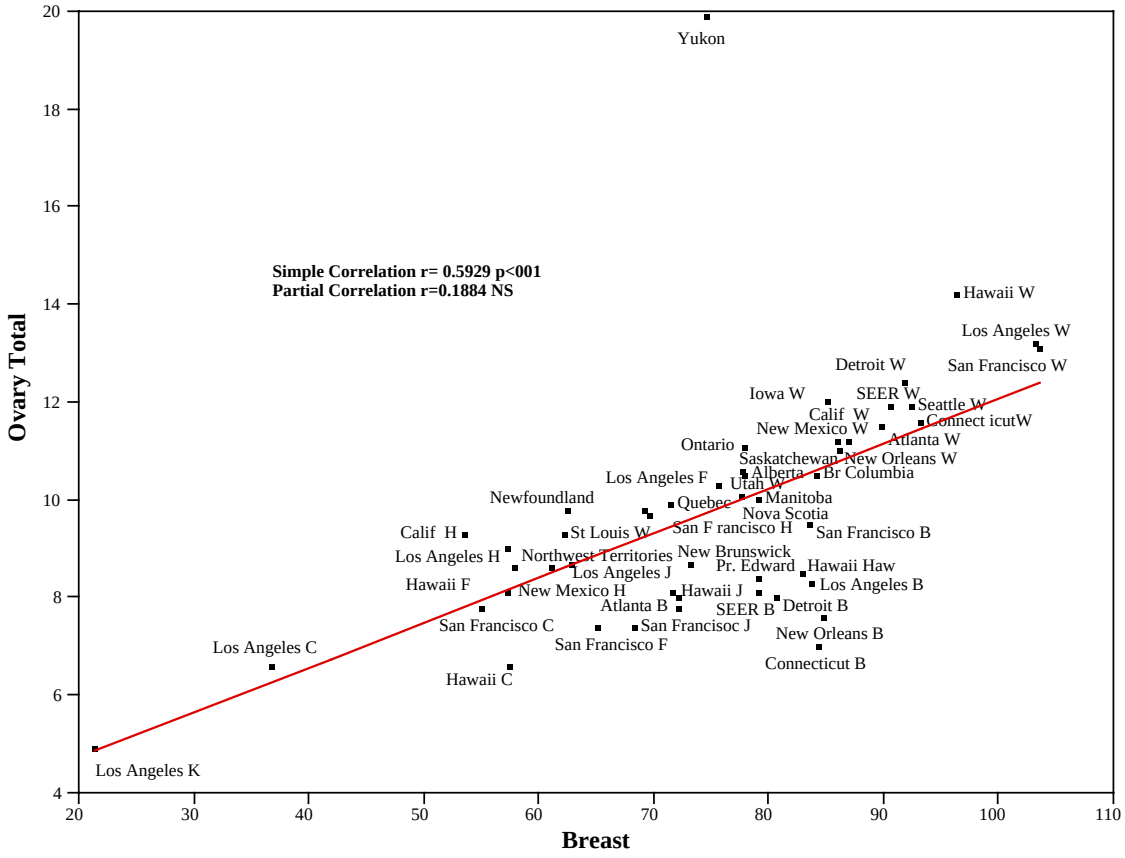

Figure 1a. Correlation Between Ovary Total and Breast Cancer in the USA

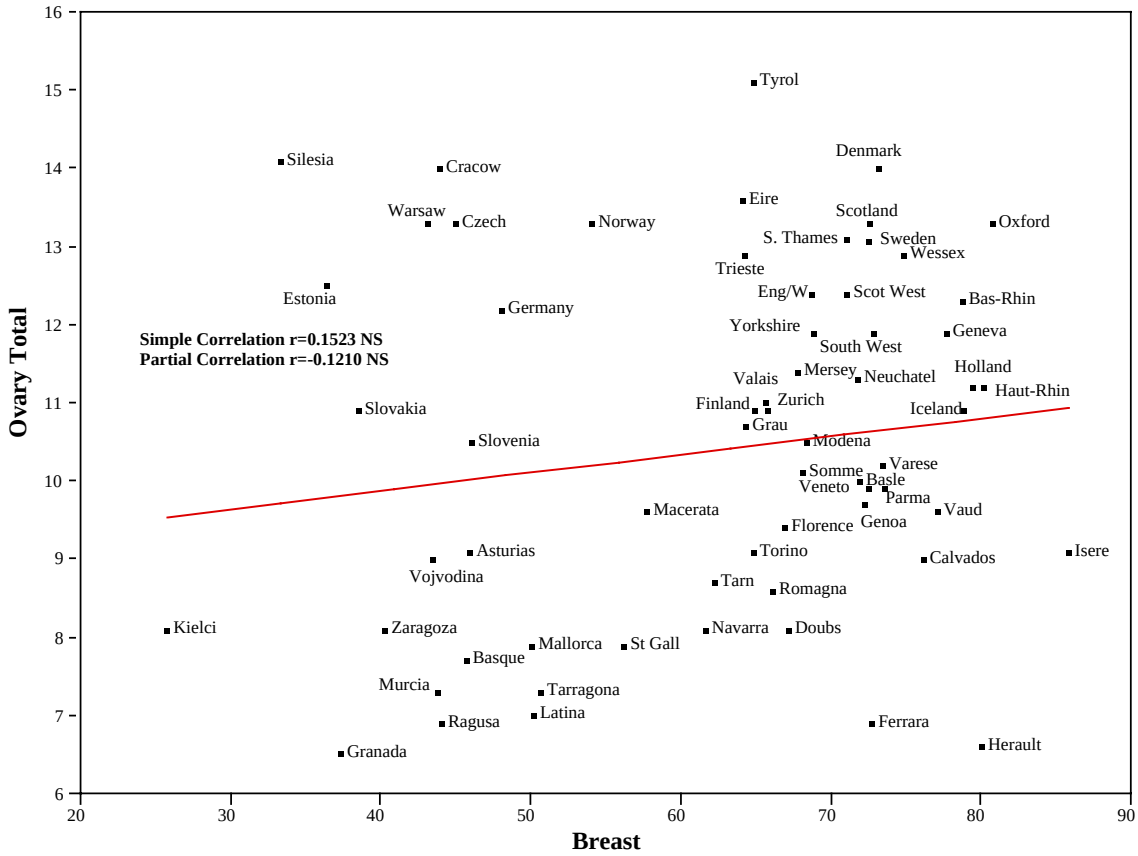

Figure 1b. Correlation Between Ovary Total and Breast Cancer in Europe

Table 2a. Correlations Between Ovarian Carcinomas and Adenocarcinomas at Different sites. North America*

Site		Ovary						Breast	Corpus	Cervix	Colon	Rectum
		Total	Serous	Mucin	Endom.	Clear	AC	AC	AC	AC	AC	AC
Ovary	Total	-	0.001	0.001	0.001	0.001	0.001	NS	NS	0.001	NS	NS
	Serous	0.001	-	-0.001	-0.001	-0.001	-0.001	NS	NS	-0.005	NS	NS
	Mucin	0.001	0.005	-	-0.005	-0.005	-0.01	-0.01	NS	NS	NS	0.005
	Endom.	0.05	NS	NS	-	0.005	-0.001	NS	NS	-0.005	NS	NS
	Clear	NS	NS	NS	NS	-	-0.001	NS	NS	-0.01	NS	NS
	AC	0.001	0.05	NS	NS	NS	-	NS	NS	-0.001	NS	NS
Breast	AC	0.001	0.005	NS	NS	NS	0.005	-	0.01	NS	0.001	NS
Corpus	AC	0.001	0.001	NS	0.01	NS	0.05	0.001	-	NS	NS	NS
Cervix	AC	NS	NS	NS	NS	NS	NS	NS	NS	-	-0.05	NS
Colon	AC	NS	NS	NS	NS	NS	NS	0.005	NS	-0.05	-	0.01
Rectum	AC	0.005	0.005	0.001	NS	NS	NS	NS	0.05	NS	NS	-

Table 2b. Correlations Between Ovarian Carcinomas and Adenocarcinomas at Different Sites Europe*.

Site		Ovary						Breast	Corpus	Cervix	Colon	Rectum
		Total	Serous	Mucin	Endom.	Clear	AC	AC	AC	AC	AC	AC
Ovary	Total	-	0.001	0.001	0.005	NS	0.001	NS	NS	NS	NS	NS
	Serous	0.001	-	-0.001	-0.005	NS	-0.001	NS	NS	NS	NS	NS
	Mucin	0.001	0.01	-	-0.05	NS	-0.001	NS	NS	NS	NS	NS
	Endom.	NS	NS	NS	-	NS	-0.001	NS	NS	NS	NS	NS
	Clear	0.05	NS	0.05	NS	-	NS	0.05	NS	0.05	NS	-0.05
	AC	0.001	NS	NS	-0.05	NS	-	NS	NS	0.05	NS	NS
Breast	AC	NS	0.05	NS	NS	NS	NS	-	NS	NS	0.001	NS
Corpus	AC	NS	0.001	NS	NS	NS	-0.05	NS	-	NS	NS	NS
Cervix	AC	0.001	NS	NS	NS	0.05	0.005	NS	NS	-	NS	NS
Colon	AC	0.05	0.01	NS	NS	NS	NS	0.001	NS	NS	-	NS
Rectum	AC	0.05	0.005	NS	NS	NS	NS	0.05	0.05	NS	0.01	-

* Lower left, simple correlations, Upper right, partial correlations . (P<?); NS, not significant.

levels than their black counterparts, while the Chinese, Filipino and Japanese have lower rates, the Koreans of Los Angeles having the lowest values. The Yukon data stand out markedly. There is a good overall correlation between ovary and breast in America, but this is less evident for the Europeans (Fig 1b) which are loosely grouped in four categories, high ovary and low breast in North-Eastern countries, high ovary and high breast in Scandinavia, Britain and parts of Switzerland, high breast and low ovary in France and Northern Italy, and finally low ovary and breast in Spain and Central Italy. How these data fit with the risk factors detailed in the first part of this paper remains to be elucidated by regional comparisons.

With division into the different subtypes, a similar picture emerges for the serous cancers, with a good correlation with breast in the US (Fig 2a). In Europe (Fig 2b) there is again a wider spread, but with Britain now lying in their high breast but low ovary serous category. An explanation for this is awaited. Serous cancers also demonstrate a good correlation with endometrial cancer of the cervix corpus in both American and European data (see Fig 3a and 3b). Again Britain is prominent for having relatively low levels for both, while Spain stands out with relatively high corpus but low ovary serous. Correlations between the other types of ovarian cancer, mucinous, endometrial, clear cell and adenocarcinoma and breast and corpus cancers are less consistent. One interesting finding is the inverse relationship found between ovary serous and adenocarcinoma in Europe, as well as America in terms of partial correlations (see Fig 4a and 4b). Clearly, no specific conclusions can be drawn from such a simplistic treatment of the data but at least we can point to the lack of unity between the different subtypes which would point to variation. This must either be in the diagnostic criteria applied or the factors which are responsible for tumor development.

Future Work and Cancer Prevention

With regard to practical prevention strategies, both primary and secondary measures can be proposed (see Fig,5). Oral contraceptives can protect even in cases with a BRCA1 or BRCA2 mutation (Narod et al., 1998). Breast feeding, hysterectomy, tubal ligation are also effective for reducing the likelihood of ovarian cancer. GnRH antagonists can reduce the spread of pelvic endometriosis (Brinton et al., 1997), and the avoidance of smoking (Doll et al., 1980), dietary supplementation (Risch et al., 1994) or talc use (Cramer et al., 1999) also reduce the initiation or growth of

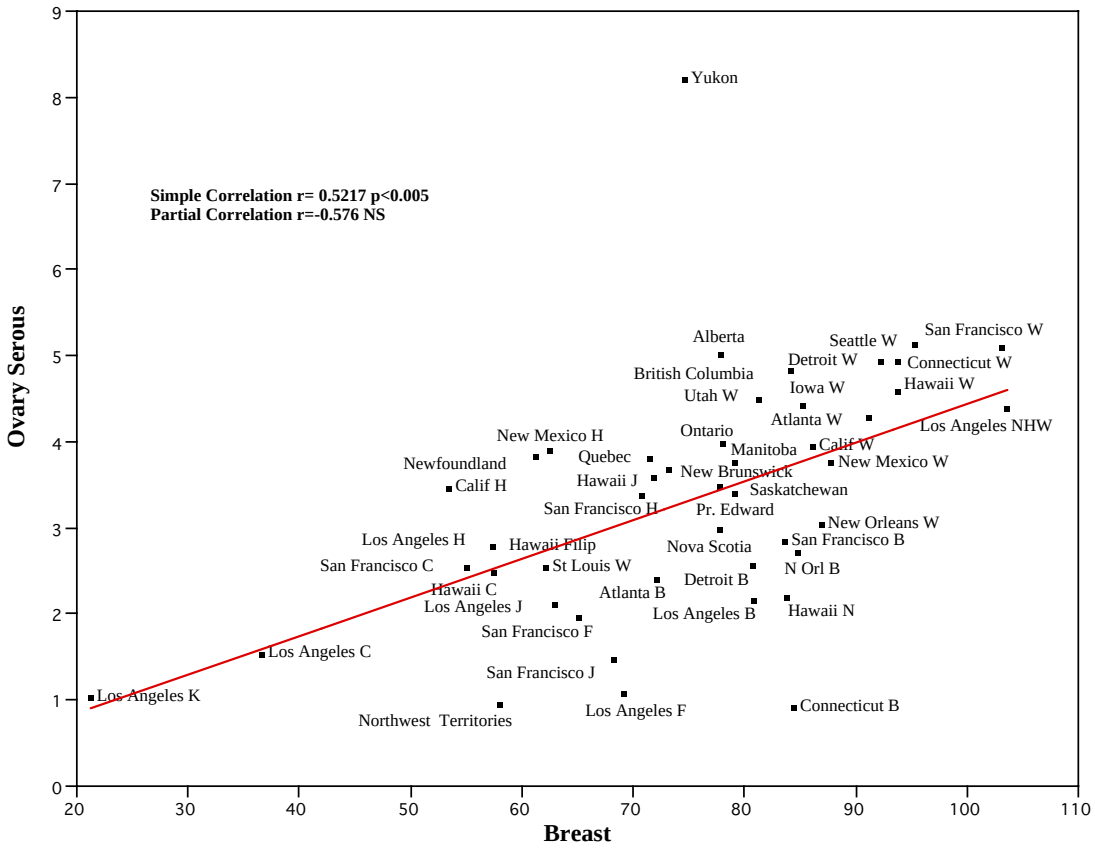

Figure 2a. Correlation Between Ovary Serous and Breast Cancer in the USA

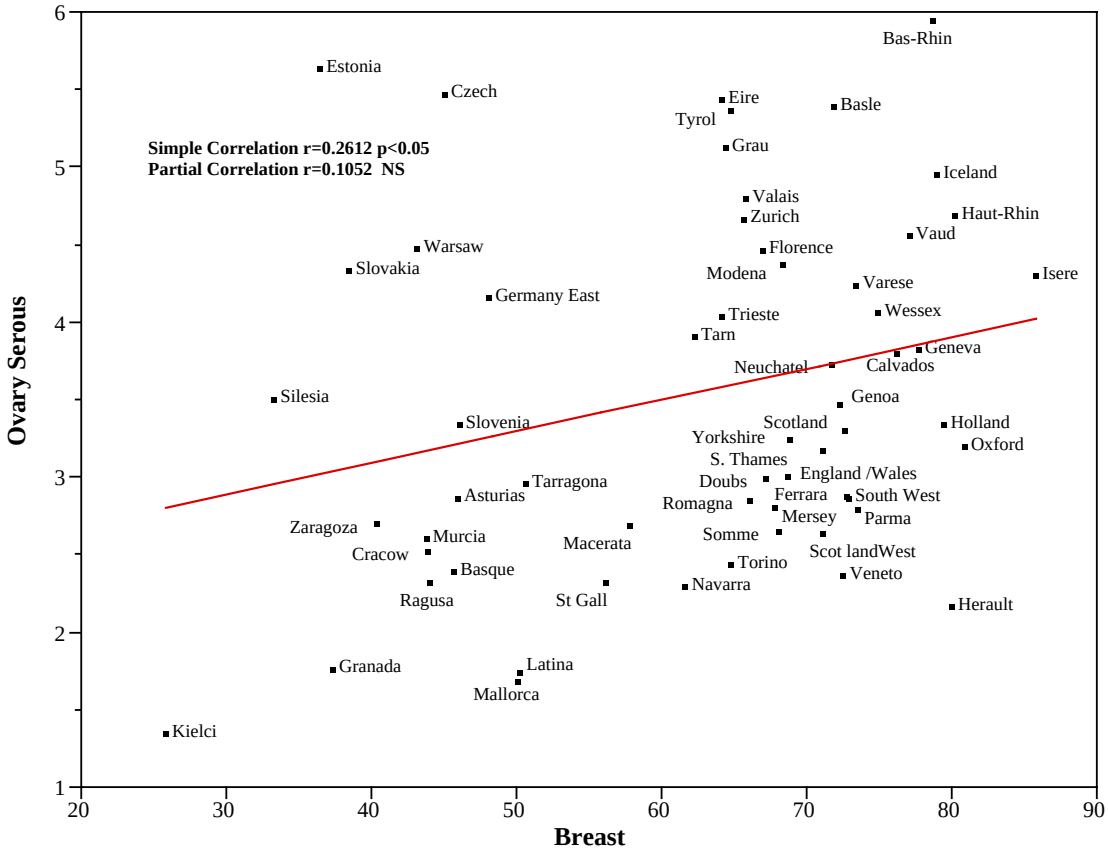

Figure 2b. Correlation Between Ovary Serous and Breast Cancer in Europe

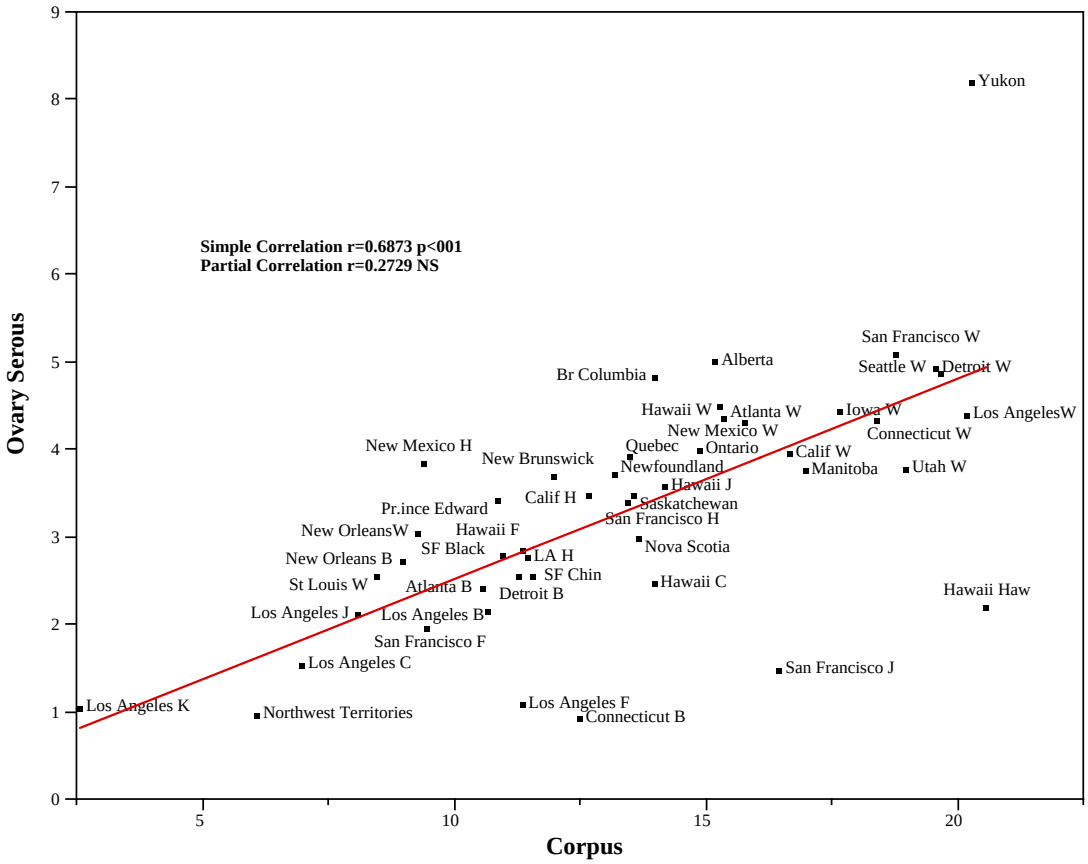

Figure 3a. Correlation Between Ovary Serous and Corpus Cancer in the USA

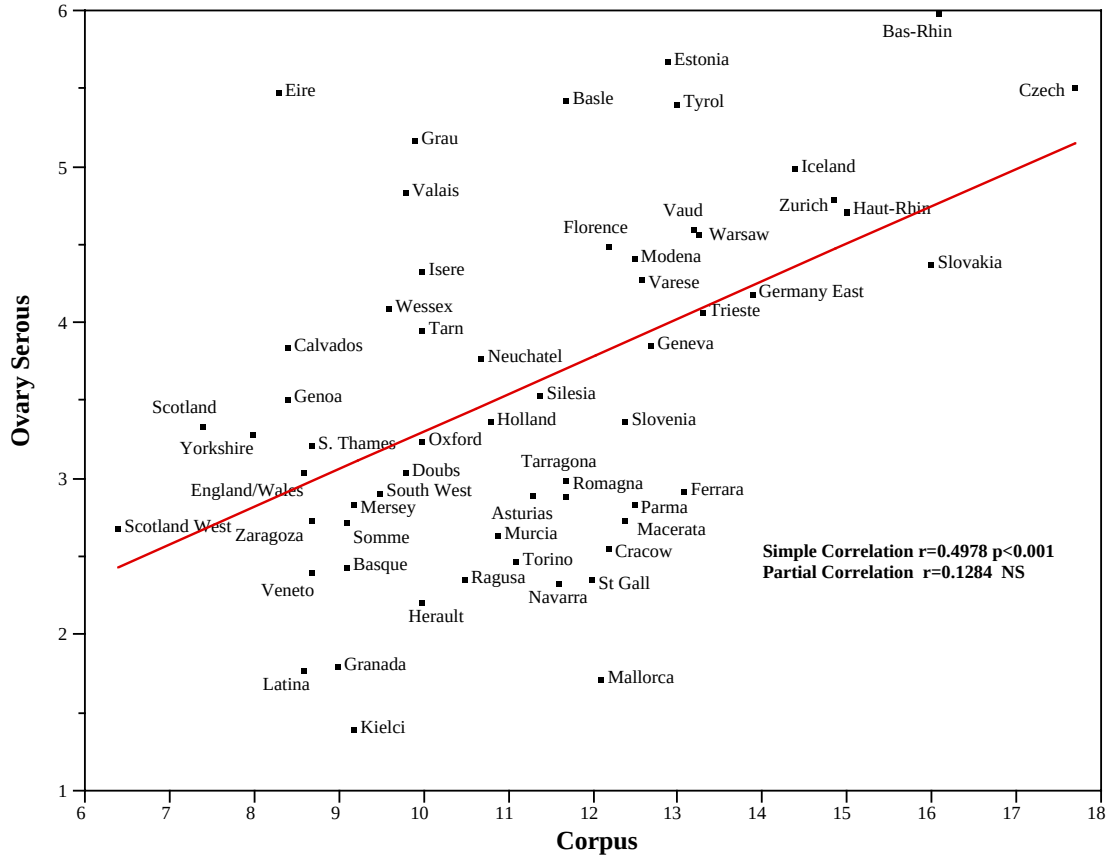

Figure 3b. Correlation Between Ovary Serous and Corpus Cancer in Europe

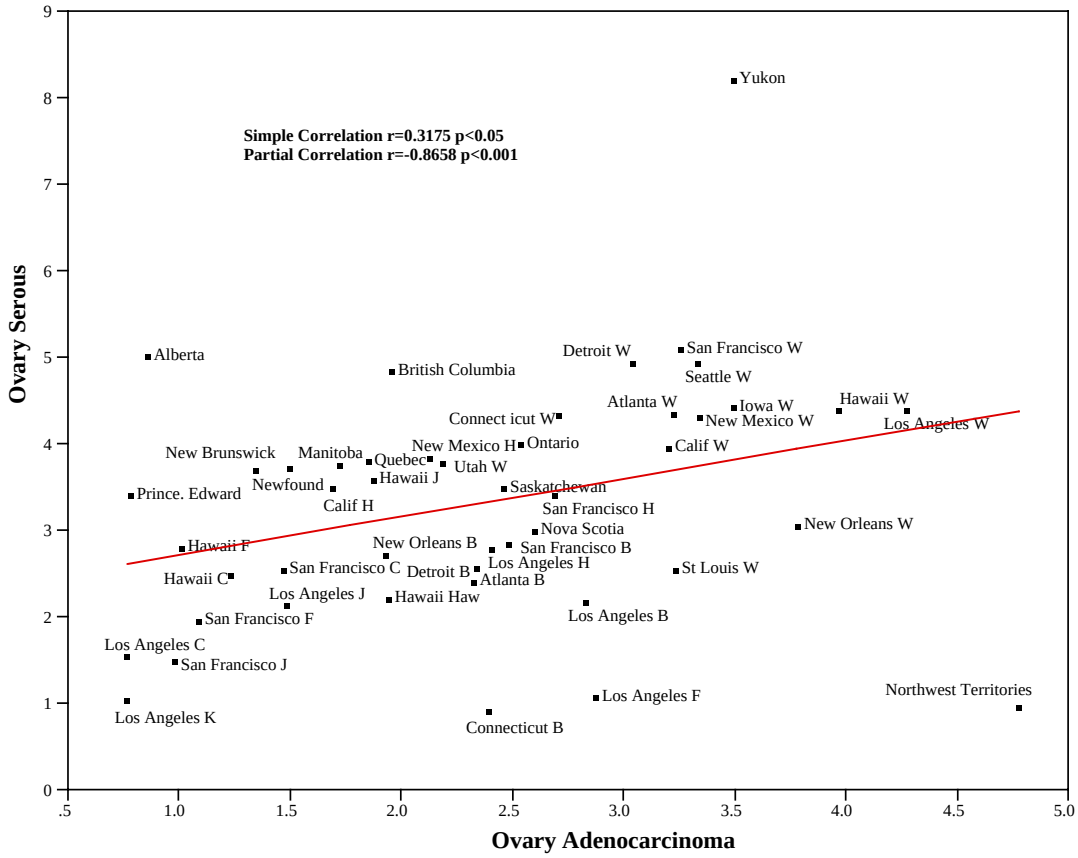

Figure 4a. Correlation Between Ovary Serous by Ovary Adenocarcinoma in the USA

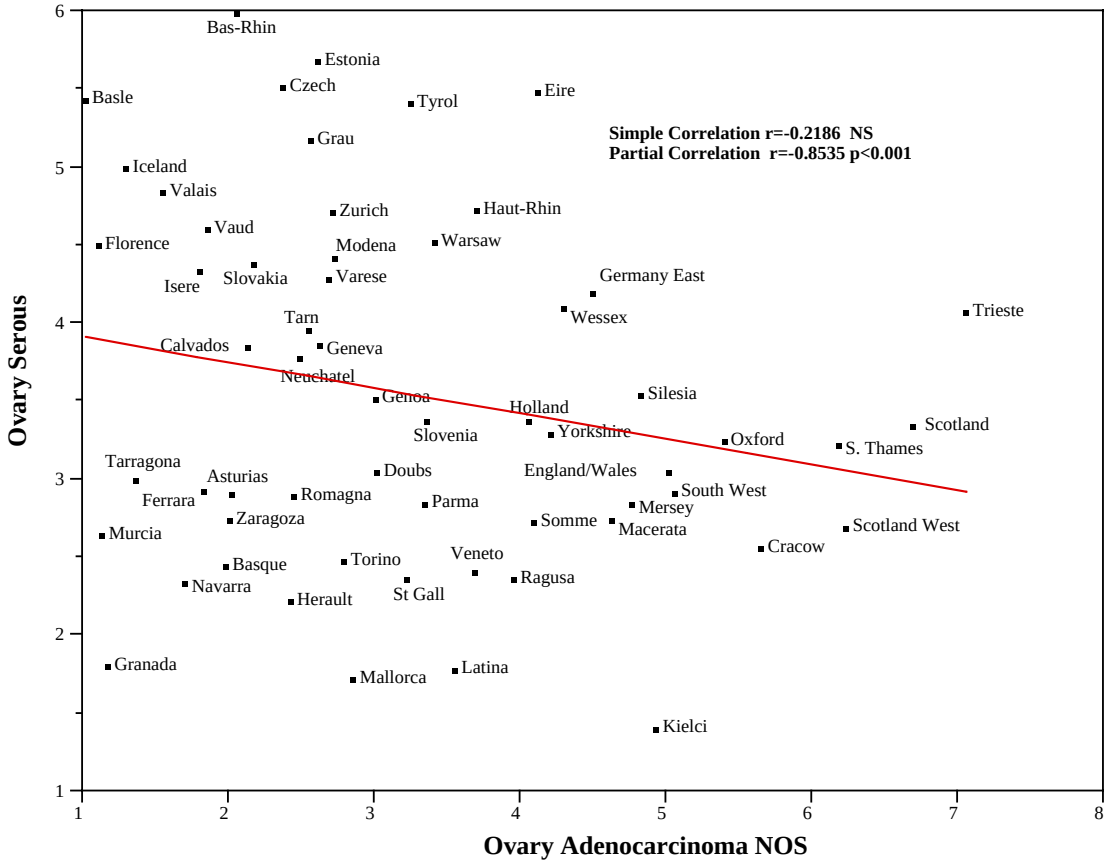

Figure 4b. Correlation Between Ovary Serous by Ovary Adenocarcinoma in Europe

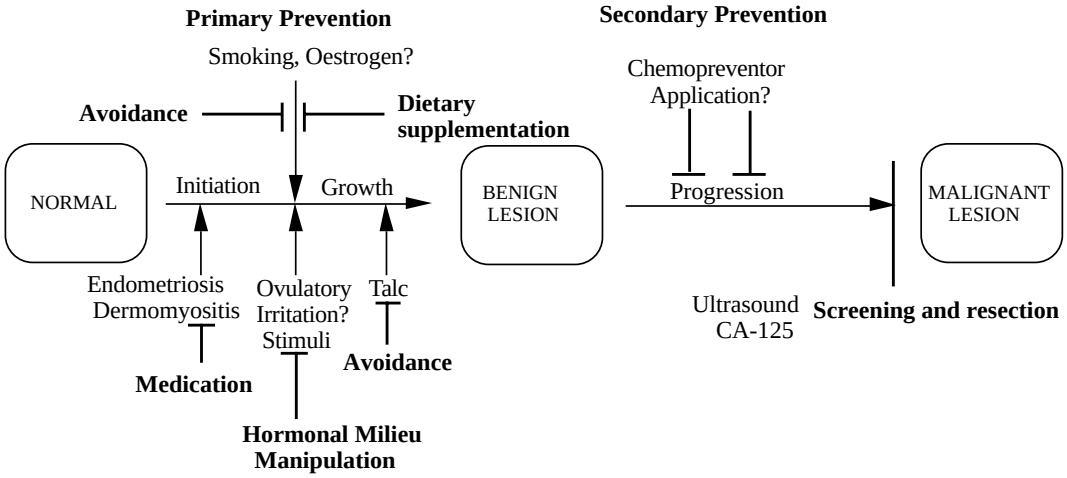

Figure 5. Interventive Strategies for Ovarian Cancer

surface ovarian epithelium. As secondary prevention, chemopreventor application such as retinoids (Guruswamy et al., 2001), will protect progression of malignant ovarian tumor and ultrasound (van Nagell et al., 1990) and CA125 (Woolas et al., 1993) at the screening and genetic testing for family history (Boyd et al., 1997) will enhance the early detection of ovarian cancer and hopefully improve survival.

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