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(Annegers, Strom et al. 1979; Axelrod, Fruchter et al. 1984; Parazzini, Negri et al. 1992; Gallion and Smith 1994; Bergfeldt, Rydh et al. 2002; Einbeigi, Meis-Kindblom et al. 2002; Negri, Pelucchi et al. 2003)

Annegers, J. F., H. Strom, et al. (1979). "Ovarian cancer: incidence and case-control study." Cancer **43**(2): 723-9.

The incidence of ovarian cancer in Rochester, Minnesota over the 40-year period 1935 through 1974 was determined; and risk factors for epithelial ovarian cancer occurring in Rochester from 1945 to 1974 were examined in 116 patients and 464 controls. Among the characteristics studied, only nulliparity was found to be a significant risk factor--relative risk 1.8. Other suspected risk factors--including hypertension, obesity, age at menopause, prior therapeutic pelvic radiation, and prior exposure to exogenous estrogen--were found not to differ significantly between patients and controls. **The ovarian cancer patients were found to have a significantly lower frequency of prior hysterectomy and of unilateral oophorectomy than the control group. Thus out data show that hysterectomy, even when one or both ovaries are preserved, is associated with a lower risk of subsequent ovarian cancer.**

Axelrod, J. H., R. Fruchter, et al. (1984). "Multiple primaries among gynecologic malignancies." Gynecol Oncol **18**(3): 359-72.

Seventy-eight synchronous or metachronous tumors among 2362 patients followed by the Downstate Gynecologic Tumor Registry are reviewed. Significant synchronous tumor pairs include cervix (invasive and in situ)-ovary, cervix (in situ)-uterus, cervix (in situ)-kidney, **endometrium-ovary**, endometrium-rectosigmoid, and **ovary-breast**. Significant metachronous pairs include cervix (invasive and in situ combined)-lung, cervix (invasive and in situ combined)-upper alimentary tract, and cervix (invasive)-rectosigmoid. In the case of in situ and invasive cervical cancer-lower genital tract, significance was determined for both synchronous and metachronous pairs. Long survival is an important factor in the appearance of a second tumor as demonstrated in patients with cervical carcinoma. Synchronous data prove to be valuable in assessing in risk of second primaries in patients surviving for short periods. The roles of cigarette smoking, hormones, immunosuppression, radiotherapy, and screening are discussed.

Bergfeldt, K., B. Rydh, et al. (2002). "Risk of ovarian cancer in breast-cancer patients with a family history of breast or ovarian cancer: a population-based cohort study." Lancet **360**(9337): 891-4.

BACKGROUND: Patients with breast cancer who have mutations in the high penetrance genes BRCA1 and BRCA2, have an increased risk of ovarian cancer. Because these mutations are rare, easily obtained information such as age and family history of breast or ovarian cancer might be preferable for assessment of ovarian cancer risk in clinical practice. **METHODS:** We linked data from the Swedish Cancer Register to the Swedish Generation Register and generated a cohort of 30552 breast-cancer patients born after 1931, with information on breast and ovarian cancer diagnosis from 146117 first-degree relatives. Standardised incidence ratios (SIRs) with 95% CIs were calculated with nationwide rates of ovarian cancer, adjusted for age and calendar year. **FINDINGS:** During a mean follow-up of 6 years, 122 incident ovarian cancers were identified in the cohort, yielding an overall SIR of 2.0 (95% CI 1.6-2.4). The risk was higher in breast-cancer patients diagnosed before the age of 40 years, with a family history of breast cancer (5.6; 1.8-13.1) or ovarian cancer (17.0; 3.5-50.0). A

consistently increased risk was noted in patients with a relative who was diagnosed before the age of 50 years, with either breast or ovarian cancer. Women with a family history of ovarian cancer have an almost 10% risk of developing ovarian cancer before the age of 70. **INTERPRETATION: In young women with breast cancer, the risk of ovarian cancer is greatly raised when a family history of breast or ovarian cancer is present. Close medical surveillance, and perhaps even prophylactic oophorectomy, might be justified in high-risk groups.**

Einbeigi, Z., J. M. Meis-Kindblom, et al. (2002). "Clustering of individuals with both breast and ovarian cancer--a possible indicator of BRCA founder mutations." *Acta Oncol* **41**(2): 153-7.

In a cohort of 60436 women with a diagnosis of invasive breast carcinoma and known to reside in Sweden in 1960, 321 had a subsequent diagnosis of ovarian carcinoma. Assuming no correlation between the two cancers, one would expect that 191 women would develop ovarian cancer (standardized incidence ratio (SIR) 1.7; 95% confidence interval 1.5-1.9). Women with breast cancer before 40 years of age were at highest risk for developing ovarian cancer (SIR 4.5). Between 40 and 49 years of age, the SIR was 1.9, and at 50 years of age or older, the SIR was 1.3. Most of the excess in ovarian cancer occurred in southern Sweden. The geographic distribution of these cases coincided with the distribution of families with known BRCA1 and BRCA2 gene mutations. **These results suggest that genetic factors account for the excess in ovarian cancer that occurs in breast cancer patients and that geographic clustering of patients who have both breast and ovarian cancer may indicate the presence of a BRCA founder mutation.**

Negri, E., C. Pelucchi, et al. (2003). "Family history of cancer and risk of ovarian cancer." *Eur J Cancer* **39**(4): 505-10.

The aim of this study was to examine the relationship between history of cancer in first-degree relatives and ovarian cancer risk. Between 1992 and 1999, we conducted a case-control study in Italy on 1031 women with epithelial ovarian cancer and 2411 women admitted to hospital for acute non-neoplastic conditions. Odds ratios (OR) were estimated using unconditional logistic regression, adjusted for age and several potential confounders. Overall, 27 cases and nine controls reported a family history of ovarian cancer (OR = 7.0; 95% confidence interval (CI) 3.1-16). The OR was 23 (95% CI 2.6-212) below age 50 years, based on 10 cases and one control only. **The risk of ovarian cancer was also increased in women with a family history of cancer of the stomach (OR = 1.5; 95% CI 1.0-2.1), intestine (OR = 1.7; 95% CI 1.2-2.4), lung (OR = 1.3; 95% CI 1.0-1.8), breast (OR = 2.3; 95% CI 1.7-3.1), lymphomas (OR = 2.3; 95% CI 1.0-5.1) and all sites (OR = 1.6; 95% CI 1.4-1.9). Our results confirm the higher ovarian cancer risk in women with a family history of ovarian and breast cancer, and suggest a few associations with other sites.**

Parazzini, F., E. Negri, et al. (1992). "Family history of reproductive cancers and ovarian cancer risk: an Italian case-control study." *Am J Epidemiol* **135**(1): 35-40.

The relation between family history of ovarian, breast, and endometrial cancer and risk of epithelial ovarian carcinoma was analyzed within the framework of a case-control study conducted from 1983 to 1989. The study included 755 cases of ovarian cancer and 2,023 controls in hospital for a spectrum of acute nongynecologic, hormonal, or neoplastic conditions in the Greater Milan area, Italy. Eighteen cases (2%) and 24 controls (1%) reported a history of ovarian cancer in a first-degree relative: The corresponding multivariate adjusted odds ratio (OR) was 1.9 (95% confidence interval (CI) 1.1-3.6). The risk of ovarian cancer was elevated in women reporting a family history of breast cancer (OR = 1.6, 95% CI 1.1-2.3), but no significant association emerged with a family history of endometrial cancer (OR = 1.3, 95% CI 0.8-1.7). When the data were stratified by family history of breast cancer, a family history of ovarian cancer was over 10 times more frequent in both cases and

controls who reported a family history of breast cancer than in cases and controls reporting no family history of breast cancer. **The estimated odds ratio for ovarian cancer associated with a family history of the disease was 2.3 (95% CI 1.1-4.5) in women not reporting a family history of breast cancer**, but no association emerged in the subgroup of women reporting a family history of breast cancer. These results confirm that a family history of ovarian cancer increases the risk of the disease, but the percentage of ovarian cancer cases explained by a family history of the disease is small: **Less than 1% of observed cases in this study could be attributed to this "family risk factor."**