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Editorial

Obesity and Ovarian Cancer

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OVARIAN CANCER is one of the most common cancers in women in Europe. In England and Wales alone nearly 4000 women die from the disease each year. In Europe in 1994 the age-standardised death rate was 115 per million making it the fifth most frequent cause of death from cancer in women [1].

Survival is poor. The 5-year relative survival rate in Europe for women diagnosed between 1978 and 1985 in the Eurocare Study was only 29.5% [2]. Age-standardised incidence in England and Wales [3] rose slightly from 10 to 12 per 100 000 per year, and similar trends are seen in many other European countries [4], while all-ages mortality was broadly stable. Age-specific mortality rates in England and Wales have declined somewhat in women under the age of 55 years, but have continued to increase in older women and similar trends have been seen in other European countries [4]. A likely explanation for at least part of this decline is increasing use of the combined oral contraceptive pill [5].

Identification of risk factors for ovarian cancer is important both for primary prevention and potentially for secondary prevention through screening. Two screening tests are currently under investigation: transvaginal ultrasound examination of ovaries [6] and the tumour marker CA125 [7]. Neither has been shown to reduce mortality from the disease [8] but randomised trials are currently in progress [9]. If such screening is shown to be beneficial, risk factors for the disease may become of value in determining which women should be invited for ultrasound or CA125 measurement.

Recent reviews of the literature [10–13] conclude that the established risk factors for ovarian cancer are age, geographic area (North America and Northern Europe at highest risk), family history of ovarian cancer, number of pregnancies (nullipara are at highest risk, pregnancy is protective) and oral contraceptive use (protective). Breast feeding, increasing age at first birth, number of incomplete pregnancies and tubal ligation/hysterectomy have been identified as protective in some studies but not others, whilst other possible risk factors are early menarche, late menopause, perineal talc use, fertility drug use, radiation, caffeine consumption, milk consumption and a history of mumps.

In a paper published in this issue of the *European Journal of Cancer*, Parazzini and colleagues (pp. 1634–1637) present results from a large case–control study of the relationships between a history of various medical conditions potentially related to female hormones and the risk of ovarian cancer. Most of the findings in the paper are negative. No relationship emerged between ovarian cancer risk and diabetes, hypertension, thyroid diseases or cholelithiasis. Moreover, since the study was large, with nearly 1000 cases and 3000 controls, confidence intervals are narrow, suggesting that there are no materially important associations between these conditions that might be useful in targeting (or not targeting) women suffering from these conditions for screening programmes.

The strongest statistically significant association found by Parazzini and his colleagues was a protective effect of a reported past history of obesity on the risk of ovarian cancer. After adjusting for age, education, parity and menopausal status, the odds ratio was 0.66 (95% confidence interval (CI) 0.52–0.85). This result is surprising since it is somewhat at odds with the published literature on obesity and ovarian cancer risk. A formal meta-analysis of studies that have investigated this relationship would be problematic, because the many different studies that have reported results use different criteria for defining obesity and because there are likely to be many case–control studies of ovarian cancer risk factors that have measured weight or body mass index but which do not report the magnitude of the association (presumably in many cases because it was not statistically significant) or just report that it was not statistically significant [14].

Among the studies that do report results, most show a positive association between obesity and the risk of ovarian cancer. Results from cohort studies are the most reliable since in such studies measures of obesity are obtained prior to the onset of disease. Two large studies of this type report results on obesity. In the Iowa Women's Health Study Cohort, Mink and colleagues [15] report a statistically significant relative risk of 2.33 (after adjustment for age, parity and family history) for the highest quartile of waist-to-hip ratio relative to the lowest quartile. No strong relationship was seen for body mass index. Lew and Garfinkel [16] report a statistically significant SMR of 163 among women with weight more than 40% above average compared with women of average weight in the American Cancer Society Cohort.

A large number of case–control studies have investigated the relationship. Farrow and colleagues [17] found a statistically

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significant positive association between ovarian cancer risk and quintiles of estimated body mass index at the age of 30 years but concluded that the association was restricted to endometroid ovarian cancer. In the Cancer and Steroid Hormone study [18] there was a statistically significant positive association between tertiles of body mass index and risk. In a case–control study of epithelial ovarian cancer in Australia, Purdie and colleagues [19] found an adjusted odds ratio of 2.00 (95% CI 1.44–2.79) for those in the top 15% of body mass index versus those in the middle 30%. Szamborski and colleagues [20] found a positive association between being currently overweight and risk of disease with the strongest association for endometroid ovarian cancer. Casagrande and colleagues [21] found an adjusted odds ratio of 2.1 ($P < 0.05$) for women with at least a 20% weight excess for a given height and a significant positive relationship between body mass index and the risk of disease. Seven other case–control studies [22–28], and a Danish record-linkage study by Møller and colleagues [29] all found positive (higher risk in the highest obesity category compared with the lowest category) but not statistically significant associations between the risk of ovarian cancer and a variety of measures of obesity.

In contrast to the large number of studies reporting positive associations between measures of obesity and risk, relatively few report negative associations. A case–control study by Wynder and associates [30] reports that ovarian cancer patients were slightly less overweight than controls but the difference was not statistically significant. Case–control studies by Hildreth and colleagues [31] and Tomao and colleagues [32] report slightly but not significantly lower average body mass index in cases than controls, whilst Byers and colleagues [33] report a borderline statistically significant ($0.05 < P < 0.1$) negative trend between quintiles of body mass index and risk of disease. Mori and colleagues [34] in a case–control study report a rate of obesity at the age of 20 years in cases of 3.8% compared with rates of 12.5% ($P < 0.05$) and 8.8% in two matched control groups.

Parazzini and colleagues found two other statistically significant associations in their study. They pay very little attention to the apparent protective effect in their study of reported hyperlipidaemia (adjusted RR 0.64, 95% CI 0.45–0.89), which is almost identical to the result for reported overweight. This association is described as of borderline significance, but it is slightly stronger than the association with reported uterine fibroids (RR 0.66, 95% CI 0.47–0.92), which is given a P value of less than 0.005.

There are a number of reasons for caution in the interpretation of Parazzini and colleagues' observed inverse association between a history of obesity and risk of ovarian cancer. The measurement of obesity in their study was reported severe overweight obtained by interviewer-administered questionnaire, and defined as 'only clinically relevant overweight', rather than past records or current measurement of weight or body mass index, as used in most of the previous studies cited here. Such a measure is more susceptible to recall bias. The authors point out that diagnosis of early ovarian cancer may be more difficult in overweight women, but no information is given on the distribution of clinical stage at diagnosis among their cases. Further, the study has been in progress for many years, and the case series would not be expected to be deficient in women with early disease (who might be overweight), since these women would be expected to have appeared in the case series in due course, with later stage disease. In addition, the results, or at least part of their statistical significance, could be explained by the fact that 30% of the controls suffered from non-traumatic orthopaedic disorders and may thus have been more overweight than the general population about which inference is being made. Finally, it could be that this finding is one of the statistically significant results that may be expected to occur from time to time just by chance. In view of the fact that most previous studies report either a positive or null relation between the risk of ovarian cancer and obesity, and of the difficulties in interpreting the results from Parazzini and colleagues, we should avoid concluding that this result reflects a genuine protective association between obesity and the risk of ovarian cancer.

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