

DEBATE

Prophylactic oophorectomy

Should prophylactic oophorectomy be performed on post-menopausal women undergoing laparotomy or laparoscopy for non-gynaecological indications?

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This short communication reflects an interdepartmental debate, at the Kaplan Medical Center, Israel, on whether or not to perform prophylactic oophorectomy in post-menopausal women undergoing laparotomy for non-gynaecological disease.

We are all agreed that prophylactic oophorectomy should not be an indication for laparotomy or laparoscopic surgery in women with no family risk of ovarian cancer. However, controversy exists on whether it should be done as a concurrent procedure during other indicated non-gynaecological surgery.

Ovarian cancer is the sixth most common malignancy in women in the US (Culter and Young, 1975). The mortality for ovarian cancer in northwestern Europe and the US is ~7.3–13 per 100 000 women, making ovarian cancer the most frequent cause of death from gynaecological malignancies, and the fifth leading cause of death from cancer in women (Heintz *et al.*, 1985).

The age-specific incidence rate increases from two per 100 000 for women in their 20s to 55 per 100 000 at the age of 70 (Culter and Young, 1975). From reports by Barber (1982) and Coppleson (1981) it can be estimated that ~1 out of 424 women will experience ovarian cancer before age 40. Results from the third National Cancer Survey indicate that one of every 70 newborn females (1.4%) will eventually have this disease (Culter and Young, 1975).

The cells of origin of ovarian epithelial cancer in human beings, which comprises some 94% of cases of ovarian cancer in the US (Weiss *et al.*, 1977), are generally agreed to be from the surface epithelium of the ovary (Hertig and Gore, 1958; Bassis, 1960; Abell, 1966). In the adult, the ovarian surface epithelium arises following invagination of the coelomic mesothelium cover of the embryonic gonadal ridge, and consists of cuboidal to low columnar pseudostratified epithelium (Perez *et al.*, 1991). This mesothelial layer is separated from the hormonally active stroma by a basement membrane and a thin, connective tissue layer, homologous to the tunica albuginea of the testis (Cramer and Welch, 1983).

The events leading to malignant transformation and progression of ovarian cells are not known. It is likely that multiple events are necessary for transformation. In the present state of knowledge, it appears that the aetiology of ovarian cancer is

multifactorial. Attempts to implicate specific agents in the aetiology of human ovarian cancer have not produced conclusive results. Epidemiological and aetiological studies have identified a group of risk factors that appears to be directly or indirectly related to human ovarian cancer. These factors can be grouped into three main categories: genetic (Lewis and Davison, 1969; Piver *et al.*, 1984; Lynch *et al.*, 1985, 1986), environmental (Graham and Graham, 1967; Cramer *et al.*, 1982) and hormonal (Stadel, 1975; Newhouse *et al.*, 1977; Harlow *et al.*, 1988). Ovarian cancer, typically, remains clinically silent until it is far advanced; morbidity and death are generally sequelae of intraperitoneal carcinomatosis. Therefore, epidemiological studies of ovarian cancer have attempted to identify risk factors that might help define groups of women at unusually high risk as it has become clear that improved prevention and detection of these groups of women are necessary.

Since there are no screening tests that are consistently accurate enough to detect ovarian cancer at an early stage, translating the current information into disease prevention requires careful clinical evaluation with a routine follow-up of patients at risk.

Attempts to improve survival and decrease the number of deaths have focused on three areas: prevention, early detection and improved treatment regimens. Currently much effort is being devoted to development of strategies for early detection. Screening programmes for ovarian cancer using pelvic ultrasonography and biochemical markers are being developed. The utility of these early-detection strategies awaits confirmation in large studies and cost-effectiveness analysis.

There are almost no data available in the literature regarding the development of ovarian cancer in post-menopausal patients who underwent laparotomy for non-gynaecological disease, where normal ovaries were not removed. It is also important to take into consideration that later occurrence of a benign ovarian disorder, e.g. benign cysts, pain or suspicion of malignancy of the ovary, can result in a re-operation rate that varies between 0.3 and 8.9% in these patients (Grundsell *et al.*, 1981).

In a study carried out by Grundsell *et al.* (1981) in Sweden, 46 patients with ovarian cancer had had previous pelvic surgery after the age of 40. Using statistical analysis, it was estimated that if prophylactic oophorectomy were a common procedure during laparotomy or hysterectomy in women over the age of 40, this would prevent 100 cases of ovarian cancer, out of 1000 diagnosed every year in Sweden. Reviewing the literature on patients who underwent pelvic surgery or hysterectomy with preservation of one or both ovaries, it was found that 466 out of 5567 (8.37%) patients with ovarian carcinoma developed ovarian cancer at some stage of their life (Table I). In a small series of studies on 2045 women aged ≥ 40 years

Table I. Frequency and percentage of previous pelvic surgery in patients with ovarian cancer

Reference	Year	Frequency	Percentage
Speer	1949	67/260	25.7
Thorp	1950	10/276	3.6
Golub	1953	9/211	4.3
Counseller <i>et al.</i>	1955	67/1500	4.5
Fagan <i>et al.</i>	1956	13/172	7.6
Bloom	1962	12/141	8.5
Grogan	1967	10/122	8.2
Terz <i>et al.</i>	1967	32/624	5.1
Gibbs	1971	28/236	11.9
Koffler	1972	45/556	8.1
Grundsell <i>et al.</i>	1981	21/352	6.0
McGowan	1987	41/291	14.1
Finazzo <i>et al.</i>	1988	16/71	22.5
Sightler <i>et al.</i>	1991	95/755	12.6
Total		466/5567	8.4

(Counseller *et al.*, 1955; Fagan *et al.*, 1956; Bloom, 1962; Terz *et al.*, 1967; Crundsell *et al.*, 1981; McGowan, 1987; Sightler *et al.*, 1991), who had pelvic or abdominal surgery leaving one or two ovaries, 78 patients (3.8%) developed ovarian cancer. In other series (Counseller *et al.*, 1955; Bloom 1962; McGowan, 1987; Sightler *et al.*, 1991), the mean age of hysterectomy was 41.0–47.0 years with a mean interval of 10.2–18.9 years between hysterectomy and ovarian cancer development. It also appears that advanced ovarian cancer can develop within 24 months of visualization of normal ovaries at surgery (Sightler *et al.*, 1991).

The decision on whether to preserve or remove the ovaries at the time of hysterectomy or laparotomy for non-gynaecological disease is influenced by a number of factors, including the primary indication for the operation, family history of ovarian cancer, possible contra-indications to hormone replacement therapy, efficacy of screening programmes for ovarian cancer, advance of laparoscopic surgical techniques and more importantly, the specific wish of each individual woman. Prior to any laparotomy, the extent of the operation, the methods to be used, and the reasons behind the choices should be clearly explained to the patients.

If access to the pelvic organ is possible, women undergoing non-gynaecological surgery during the menopausal period should be encouraged to consider prophylactic oophorectomy. The indications and decision process discussed above should be applied equally, giving proper attention to any family history of ovarian cancer.

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Is screening and/or prophylactic oophorectomy for ovarian cancer of value in high risk women?

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Shoham (1997) argues that prophylactic oophorectomy should be considered in women undergoing incidental operative procedures. In reviewing the literature, it was noted that epithelial ovarian cancer is not rare and is often disseminated at the time of diagnosis, resulting in a poor prognosis. Furthermore, it was noted that up to 8% of ovarian cancers were diagnosed after prior gynaecological operations, such as hysterectomy.

Certainly epithelial ovarian cancer is a devastating disease, but is a policy of routine prophylactic oophorectomy a desirable or beneficial public health policy? Such a policy could be argued for if, upon institution, there was a demonstrable reduction in the incidence of the disease. There should also be no medical disadvantages from oophorectomy. Finally, as a matter of public health, the policy must be cost effective, when the costs of widespread prophylactic oophorectomy are weighed against the savings from disease.

Are there any adverse consequences from routine oophorectomy? If performed incidentally at the time of laparotomy, one would generally expect no additional morbidity from performing oophorectomy at the same time. If, however, the procedure is primarily for the process of oophorectomy, then morbidity and mortality, no matter how low this might be, must be considered. At a population level, morbidity and mortality in this circumstance might become a significant factor.

Is there a demonstrable reduction in ovarian cancer prevalence when ovaries are consciously left *in situ*? The incidence of ovarian cancer in women with prior hysterectomy is ~0.2% in many studies (Mattingly and Thompson, 1985), implying that >500 oophorectomies would be required to prevent one ovarian carcinoma. Indeed, the incidence of ovarian cancer in women with prior hysterectomy is considerably lower than in the general population (Garcia and Cutler, 1984). This may be due to reduced blood supply following removal of the uterus, or in part due to simple inspection of the ovaries.

A further issue is whether there are any endocrinological disadvantages from oophorectomy. Pre-menopausal oophorectomy results in a significant increase in the risk of developing osteoporosis (Lindsay *et al.*, 1980). Although oestrogen production by the ovary falls precipitously after the menopause, androstenedione and testosterone production continue (Judd *et al.*, 1974), with peripheral conversion to oestrogen. The continued production of these androgens may also contribute to libido and the well-being of the post-menopausal woman (Garcia and Cutler, 1986). The post-menopausal ovary cannot therefore be considered a functionless organ of no value.

A second approach to reducing the population incidence of

epithelial ovarian cancer is to institute a screening programme. As with other cancer screening programmes, any proposed test must have adequate sensitivity and specificity, be simple and easy to perform, it must reach and be utilized by the target population and must be cost effective. The combined use of post-menopausal pelvic ultrasound and CA 125 assessment has been investigated as a screening tool for ovarian cancer (Jacobs *et al.*, 1993). The specificity was found to be high, but sensitivity was only fair (57.9% at 2 years). Thus a number of cases of the disease would be missed by this screening technique. It has further been suggested that routine screening using CA 125 and sonography would increase the life expectancy in the population by <1 day (Schapira *et al.*, 1993).

There appears to be scant evidence then for a practice of either routine screening using current techniques, or of prophylactic oophorectomy, applied to the entire population. Is there a case, however, for considering either measure in certain high risk groups? It has been argued that prophylactic oophorectomy be strongly considered in patients with familial ovarian cancer (Kerlikowske *et al.*, 1992). Should this approach be taken with women whose historical (rather than genetic) background would suggest a higher relative risk for this disease?

Epidemiological studies have indicated significantly raised relative risk values for women with a past history of infertility, presumably on the basis of repeated uninterrupted ovulation. In contrast, women with interrupted ovulation as a result of contraceptive pill usage, pregnancy and breast feeding appear to have a decreased relative risk of developing ovarian cancer. Amongst women with a history of infertility, a quite significant increase in relative risk in those who additionally give a history of fertility agent usage has been reported (Whittemore *et al.*, 1992), although the specific association of fertility drugs has been questioned (Balasch and Barri, 1993). An increase in the incidence of borderline ovarian tumours has been reported with prolonged clomiphene usage (Rossing *et al.*, 1994). Determining the contribution of the fertility agents used, in contrast to the underlying influence of infertility and other historical factors *per se* has been difficult to ascertain. Venn *et al.* (1995), in a retrospective comparative study of women referred for in-vitro fertilization (IVF), found no significant differences in the incidence of ovarian or uterine cancer between women referred who ultimately had stimulated IVF and those who did not. Nonetheless, the incidence of both cancers was increased in women with unexplained infertility in both groups.

If the relative risk of ovarian cancer is raised in women with a history of infertility, and in the absence of definitive evidence that ovulation agents are non-contributory, should workers in the field of infertility offer screening and/or prophylactic oophorectomy to their clients? If, for example, the relative risk for ovarian cancer amongst women with unexplained infertility is increased 19-fold (Venn *et al.*, 1995), relative to those with other forms of infertility, CA 125 and ultrasound screening may yet prove to be beneficial and cost effective within this subset. Additionally, there might be a more powerful argument for prophylactic oophorectomy, particularly in circumstances of incidental laparotomy or

hysterectomy for benign disease. Women with a past history of IVF treatment would comprise an ideal group for a prospective analysis of the value of ovarian cancer screening in a selected subpopulation.

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Prophylactic oophorectomy on post-menopausal women

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The article by Shoham (1997) on prophylactic oophorectomy raises an old question. About two decades ago we had the same discussion in The Netherlands. At that time it was customary to remove the ovaries whenever a woman aged ≥ 45 years was operated on by a gynaecologist. We had a hard time convincing our teachers that ovaries at the time of the menopause, and for a length of time thereafter, were still a prized possession. The reasoning of our elders was that once the ovaries were removed, no grim disease such as ovarian cancer (a cancer that is almost always beyond control at the time of detection) could develop.

Since Shoham (1997) quotes several references from some time ago, it seems logical that he would reach the same

conclusion as those who ruled the operating room at that time. Surely the question addressed is somewhat different, that of prophylaxis in non-gynaecological surgery and specifically in post-menopausal women. The article steers towards a positive answer to the title question, but this is over-shadowed by the number of factors to be taken into account.

Although most gynaecologists would nowadays consider prophylactic oophorectomy in selected cases, the most important indication, linked to a positive familial history of ovarian cancer, is not related to the hormonal status of the women in question nor to the type of possible concurrent surgery, but to those (rare) cases where the odds ratio of developing ovarian cancer is >40 (Boente *et al.*, 1995). In our clinic, we have performed prophylactic oophorectomy in women aged <30 years who carry BRCA1, the gene predisposing to breast and ovarian cancer, the risk of the latter being estimated at 40–63% (Easton *et al.*, 1995). We realize that ovarian cancer can still occur in the lining of the abdominal cavity, even when the removed ovaries are tumour-free, although the risk is probably a few percent (Eeles, 1996).

If there was safety in numbers, we would have agreed long since, but there is none. In The Netherlands we have 1300 new cases of ovarian cancer each year, in Britain the number is 5100 (Eeles, 1996), and in the US 21 000 (Boente *et al.*, 1994). Of these, 5% are thought to be hereditary, and 95% sporadic. The hereditary cancers tend to appear earlier in life than sporadic cancers, since one of the cancer-causing mutations is present in all body cells at birth. When focusing on post-menopausal women, we would agree that, at the age when we would advise prophylactic oophorectomy, most ovarian cancers are still to come. However, even with the increase in age-specific incidence rate to 55 per 100 000 at the age of 70, we would have to perform a vast number of prophylactic oophorectomies to put a dent into the yearly incidence figures; certainly many more than the ones we would encounter at random during non-gynaecological surgery.

The series reported in the literature quoted by Shoham (1997), dealing with ovarian carcinoma after previous abdominal surgery, are crowded with pre-menopausal women and do not support the case at hand. Compilation of different reports, with different starting points, into one table, is risky.

I agree with Dr Shoham on the fact that adequate preoperative screening is not available. A test with 100% sensitivity would need 99.9% specificity to have a positive predictive value of only 10%. Reports on the use of colour-flow Doppler ultrasonography are encouraging, but more information needs to be gathered on the specificity of transvaginal sonography, especially in small ovarian cancers (Boente *et al.*, 1994). Laparoscopy alone is not sufficient to rule out malignancy. If we plan on prophylactic oophorectomy during non-gynaecological laparoscopic surgery, we need to be certain that no malignancy exists. As we have just agreed on the inadequacy of pre-operative screening, we would get into a circular argument, so I will leave laparoscopy out of the debate for now.

We have to look at the downside of prophylactic oophorectomy as well. Apart from morbidity and mortality (hopefully, both of which are very low), removal of the ovaries has other (side-)effects that cannot be neglected. Sexology and

endocrinology have taught us that androgen production in the ovarian stroma hardly diminishes after the menopause (Bachmann, 1995), unless the ovary becomes fibrotic (Davis and Burger, 1996). When sexology was in the limelight, libido was thought to be severely hampered in ovariectomized women, for lack of androgens. Doubts were raised about this, when libido was mistaken for sexual initiative, although it was known that decreasing libido in the male might be a more decisive factor. Recent findings support the latter statement (Rosen *et al.*, 1994). Stromal production of androgens is not only relevant in polycystic ovarian disease (Insler *et al.*, 1993), it can account for up to 50% of post-menopausal testosterone production (Davis and Burger, 1996). A decline in androgen production may develop very gradually under normal circumstances, but if it occurs after oophorectomy, symptoms of reduced sexual function, loss of energy, and negative effects on bone mass may become manifest. Since not all women would tolerate hormone replacement therapy if needed after prophylactic oophorectomy, would we then be responsible for sending them off into the future with brittle bones?

Dr Shoham deserves credit for raising an important question once again. It stimulates our efforts in identifying the patients at risk, a subject confused by many variables such as age, parity, oral contraceptive use, infertility, and tubal ligation, not to mention coffee use. It would be unrealistic to ask our colleagues in the other surgical departments to identify the post-menopausal women with a particular risk of developing ovarian cancer. All we can ask them to do, is to identify the woman with a positive familial history of ovarian cancer, so that we can provide proper counselling.

A positive familial history seems to be the only remaining indication for prophylactic oophorectomy in post-menopausal women, undergoing non-gynaecological abdominal surgery.

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Prophylactic oophorectomy: a century long dilemma

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As early as the beginning of the 20th century, the issue of ovarian conservation during hysterectomy was ardently debated. In the 1930s, the dilemma was whether hysterectomies, even with the preservation of ovaries, produce menopausal symptoms (Sessums and Murphy, 1932a,b; Dippel, 1939). Fortunately, basic science has answered this question. Yet, as we approach the end of the 20th century, the same debate continues, although now the dilemma is whether prophylactic oophorectomies during benign abdominal or pelvic surgery are justified to prevent subsequent re-operation of retained ovaries, especially in the prevention of ovarian cancer, the most fatal of all gynaecological malignancies.

Epithelial ovarian cancer (EOC) is the second most common malignancy of the female genital system. EOC accounted for 26 600 cases and 14 400 deaths in 1995 (Wingo *et al.*, 1995). Women at greatest risk of developing EOC are those: (i) with a family history of ovarian cancer; (ii) are nulliparous; and (iii) with no history of using oral contraceptives. The peak incidence of EOC is at age 64 (Berek and Haker). The incidence of ovarian cancer increases with age: in women aged <30 years, the incidence is 5/100 000; at age 30–50 years, 21/100 000; aged >50 years, 37/100 000; and aged >60, 46/100 000 (National Cancer Institute, 1990). Despite the achievements which have been made in the treatment of ovarian cancer, it continues to have the highest fatality to case ratio of all gynaecologic malignancies (Cramer and Cutler, 1974). In the past 30 years, the 5 year survival in advanced ovarian cancer remains <30% (Silverberg, 1985). In the past decade, the number of women dying of ovarian cancer in the US has increased 18% (Adonakis *et al.*, 1996).

Prevention and early detection

Prevention and early detection are two measures which may reduce the mortality of ovarian cancer.

Efforts are being made to develop strategies for the early detection of ovarian cancer. Potential screening tests include pelvic exams, sonography (transabdominal and transvaginal) and tumour marker measurements (CA 125); however, large prospective studies and cost analyses are still needed to confirm the utility of these screening tests (Einhorn *et al.*, 1986; Jacobs *et al.*, 1988; Adonakis *et al.*, 1996).

Since the 1950s, the issue of prophylactic oophorectomy during benign pelvic or abdominal surgery has been plaguing the surgeon. Studies have confirmed that 4.5–14.1% of women develop ovarian cancer after hysterectomy for non-ovarian conditions (Counsellor *et al.*, 1955; Terz *et al.*, 1967; McGowan, 1987; Gibbs, 1971). Similarly, data from the American College of Surgeons demonstrated that among 12 316 patients with

ovarian cancer, 18.2% had previous hysterectomies with conservation of one or both ovaries and 57.4% of these women were over the age of 40 (Averette *et al.*, 1993). Development of ovarian cancer occurred 13 months to 49 years after hysterectomy. Using their experience from the University of Miami and those of three similar studies, Sightler *et al.* (1991) reported that prophylactic oophorectomy would have prevented 138 out of 2632 cases (5.2%) of ovarian cancer in women who underwent hysterectomy at the age ≥ 40 years. Considerations have been made to conserve the ovaries during pelvic surgery to prevent menopausal symptoms; however, studies suggest that retained ovaries may not provide prolonged ovarian function. To support the latter contention, in the 1930s, Sessums and Murphy (1932a) demonstrated that among 91 women aged < 36 years who underwent hysterectomy with ovarian preservation, 92.5% experienced the onset of menopausal symptoms within 2 years after surgery. Moreover, Siddle *et al.* (1987) documented that 34% of women who underwent hysterectomy with conservation of the ovaries developed menopausal symptoms within 1–2 years. Lower bone density was significantly reduced in pre-menopausal women with ovarian preservation at the time of hysterectomy (Watson *et al.*, 1995).

Advantages and disadvantages

The advantages and disadvantages of prophylactic oophorectomy need to be addressed. Poor self image and surgically induced menopause are potential disadvantages of prophylactic oophorectomy. In the past 20 years, studies have confirmed that not only does hormone replacement therapy relieve menopausal symptoms such as hot flushes, night sweats and vaginal dryness but it also has well documented beneficial effects towards the cardiovascular system, the bones, and the lipoprotein profile (Lindsay *et al.*, 1976; Ross *et al.*, 1981; Ravnika, 1990). If hormone replacement therapy is contraindicated, progestational agents or clonidine may relieve vasomotor symptoms (Ravnika, 1990), and Fosamax can lessen the chance of osteoporosis. Thus with the proven benefits of hormone replacement therapy, surgical menopause should not be of a concern to the patient and physician.

Potential advantages of prophylactic oophorectomy are prevention of ovarian cancer and the prevention of the residual ovarian syndrome. Oral contraceptives have been shown to decrease the risk of developing EOC; however, patients may be reluctant to use oral contraceptives because of inconvenience, weight gain, and abnormal vaginal bleeding (Rosenberg *et al.*, 1994); thus, prophylactic oophorectomy is the only measure known to eliminate the risk of developing EOC. Patients with residual ovary syndrome present with chronic pelvic pain, asymptomatic pelvic mass and dyspareunia (Christ and Lotze, 1975). In all, 0.9–5.2% of patients with conserved ovaries will require re-operation for adnexal disease (Grogan and Duncan, 1955; Ranney and Abu-Ghazaleh, 1977). Prophylactic oophorectomy can eliminate re-operation of the residual ovaries and its additional risk from anaesthesia.

Conclusion

Prophylactic oophorectomy during benign pelvic/abdominal surgery is recommended for women who have a significant

family history of ovarian cancer and have completed child bearing or for women aged > 40 years. Prophylactic oophorectomy can prevent ovarian cancer, a chronic fatal disease in search of a better prognosis.

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