A meta-analysis was applied to the published case-control studies of ovarian cancer in order to examine the association of tubal sterilization and induced abortion with ovarian cancer. Among 65 case-control studies published between 1981 and 1991, six articles reported the numbers of women who underwent tubal sterilization and four articles reported the numbers of women undergoing induced abortion in both cases and their controls. The test for combinability of these 6 or 4 odds ratios revealed that these odds ratios were combinable in terms of tubal sterilization or induced abortion. It was shown that tubal sterilization was significantly associated with a reduced risk for ovarian cancer (the summary odds ratio = 0.55, 95% confidence interval or 95% CI 0.45-0.68), even after excluding nulliparous women from the analysis (the summary odds ratio = 0.52, 95% CI 0.36-0.74), and that induced abortion was also related to a decreased risk for ovarian cancer (the summary odds ratio = 0.81, 95% CI 0.63-1.04 based on the 4 combinable odds ratios; the summary odds ratio = 0.64, 95% CI 0.46-0.89 based on the 2 studies in Asian countries). Several etiological inferences were made with regard to these findings, and some proposals for further research were addressed in ovarian cancer epidemiology. J Epidemiol, 1992; 2: 111-118.

Risk factors for ovarian cancer have been extensively assessed around the world by analytical epidemiology as well as by descriptive epidemiology. For instance, a number of case-control studies and several cohort studies on ovarian cancer were conducted and published during the recent decade 1981-1991. According to these studies, women with a smaller number of livebirths have been consistently found as a high-risk group for ovarian cancer. Family history of ovarian or breast cancer and frequent consumption of high-fat foods have been suggested as risk factors as well. Conversely, use of oral contraceptives (OC) has been indicated as protective against ovarian cancer.

There have been several case-control studies suggesting tubal sterilization (TS) and/or induced abortion (IA) being associated with a reduced risk for ovarian cancer. However, the reported odds ratios (ORs) with regard to TS or IA show considerable variation with a wide range of 95% confidence interval (95% CI) across case-control studies. It seems, thus, worthwhile to perform a meta-analysis on the relationship of TS or IA to ovarian cancer.

The MEDLINE was used as the source of identifying published case-control studies on ovarian cancer. Sixty-five such studies were published between 1981 and 1991. We set 3 criteria to define eligibility for the present meta-analysis of ovarian cancer: 1) Ovarian cancer was confirmed histologically and confined to common epithelial origin, 2) Sample sizes of both cases and controls should exceed a hundred, 3) The numbers of cases and controls who underwent TS or IA were reported. Eight articles met our 3 criteria. Among them, reported the number of women who underwent TS, that of women who experienced IA, as well as the numbers of women who experienced both TS and IA.
The combinability of ORs across studies was evaluated, and if the studies were found to be combinable, a summary odds ratio and its 95% CI were calculated by the method of Fleiss and Gross. Point and interval estimates of the odds ratio in each study were computed with the program presented by Rothman.

**TUBAL STERILIZATION (TS) AND OVARIAN CANCER**

Six studies reported the numbers of women who underwent TS in both cases and controls. Table 1 gives a brief explanation of these 6 studies, including years and areas of survey, the numbers of cases and controls, the numbers of tubo-sterilized women, and so on. As shown in an upper part of Fig. 1, 5 of the 6 articles showed that TS was significantly associated with a reduced risk of ovarian cancer. The test for combinability of the 6 ORs for TS in these articles revealed that these ORs were combinable (chi-square = 10.34, d.f. = 5, not significant or NS). The summary OR for TS was 0.55 (95% CI 0.45-0.68, p < 0.001).

Assuming that none of the nulliparous women underwent TS, nulliparous women in both cases and controls should be excluded from the analysis. Because the actual numbers of either nulliparous cases or controls were not reported in the 3 reports, the residual 3 studies were able to be meta-analyzed excluding nulliparous women. The test for combinability of the 3 ORs excluding nulliparous women showed that these ORs were combinable (chi-square = 0.25, d.f. = 2, NS). As shown in a lower part of Figure 1, the summary OR for TS excluding nulliparous women was 0.52 (95% CI 0.36-0.74, p < 0.001).

Mori et al. showed that TS was inversely associated with the risk of ovarian cancer (crude OR = 0.40, 95% CI 0.18-0.81; adjusted OR = 0.47, 95% CI 0.21-1.00, adjusted for marital status, the number of livebirths, and IA). However, the trend of relationship between duration of TS and the reduced risk was not evaluated in this study, though it was shown that the average age at TS among the cases (31.5 years) was quite similar to that among the controls (31.8 years).

Whittemore et al. reported that TS was related to a reduced risk of ovarian cancer (OR = 0.53, 95% CI 0.28-0.95), and that the magnitude of this relation was not substantially altered even when the number of livebirths was controlled (OR = 0.56, p = 0.07). They also showed that the risk for women tubo-sterilized within 10 years before interview was 0.35 (95% CI 0.12-1.02), while the risk for women tubo-sterilized more than 10 years before interview was 0.69 (95% CI 0.32-1.50). Accordingly, they did not find the trend of relationship between duration since tubo-sterilization and a decreased risk for ovarian cancer.

Shu et al. noted that TS was associated with a decreased risk of ovarian cancer (OR = 0.46, 95% CI 0.25-0.82), while this association became insignificant after the number of livebirths, education, history of ovarian cyst, and age at menarche were adjusted (OR = 0.8, 95% CI 0.4-1.6), and that there was no obvious trend between years since tubo-sterilization and the decreased risk for ovarian cancer. Irwin et al. stated that the significantly lowered ovarian cancer risk remained for up to 15 years after TS, but appeared to be temporary.

Table 1. The published case-control studied on ovarian cancer which explained the number of women who underwent tubal sterilization.

<table>
<thead>
<tr>
<th>Reference no.</th>
<th>32</th>
<th>34</th>
<th>39</th>
<th>41</th>
<th>51</th>
<th>58</th>
</tr>
</thead>
<tbody>
<tr>
<td>First author</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survey area</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>200</td>
<td>110</td>
<td>188</td>
<td>235</td>
<td>172</td>
<td>469</td>
</tr>
<tr>
<td>Age restriction</td>
<td>&lt;70 yrs.</td>
<td>15-85 yrs.</td>
<td>18-74 yrs.</td>
<td>&lt;65 yrs.</td>
<td>18-70 yrs.</td>
<td>100%</td>
</tr>
<tr>
<td>Response rate for cases</td>
<td>96%</td>
<td>99%</td>
<td>88%</td>
<td>94%</td>
<td>100%</td>
<td>71%</td>
</tr>
<tr>
<td>No. of controls</td>
<td>211</td>
<td>220 (100+110) hospitals+screening 100%</td>
<td>539 (280+259) hospitals+population 72%</td>
<td>451 hospitals</td>
<td>172 population</td>
<td>4086 population</td>
</tr>
<tr>
<td>Source of controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response rate for controls</td>
<td>42%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. in cases</td>
<td>18</td>
<td>39</td>
<td>36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. in controls</td>
<td>13</td>
<td>74</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubo-sterilized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. in cases</td>
<td>48</td>
<td>10</td>
<td>3</td>
<td>21</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>No. in controls</td>
<td>60</td>
<td>44</td>
<td>71</td>
<td>45</td>
<td>40</td>
<td>661</td>
</tr>
</tbody>
</table>
Sterilization, Abortion & Ovarian Cancer

1) Nulliparous women included:
Koch et al.
Mori et al.
Whittemore et al.
Booth et al.
Shu et al.
Irwin et al.

Summary

<table>
<thead>
<tr>
<th>0.03</th>
<th>0.1</th>
<th>0.5</th>
<th>1.0</th>
<th>2.0</th>
<th>log odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.55 (0.45-0.68) #</td>
</tr>
</tbody>
</table>

2) Nulliparous women excluded:
Mori et al.
Whittemore et al.
Shu et al.

Summary

<table>
<thead>
<tr>
<th>0.2</th>
<th>0.5</th>
<th>1.0</th>
<th>2.0</th>
<th>log odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.52 (0.36-0.74) #</td>
</tr>
</tbody>
</table>

Figure 1. The summary odds ratio of ovarian cancer due to tubal sterilization. #: The summary odds ratio with 95% confidence interval.

wane thereafter. Thus, there was no evidence of a trend relating duration since tubo-sterilization to a reduced risk of ovarian cancer.

The findings mentioned above may indicate that the inverse relation between TS and ovarian cancer is brought about through a confounding factor such as subfertility, because subfertility reduces parity which is positively associated with TS and is negatively associated with the risk of ovarian cancer.

Although it is less likely, two distinct mechanisms have been suggested to support that TS directly prevents the occurrence of ovarian cancer. Firstly, Woodruff[75] mentioned that possibly some agent enters the peritoneal cavity through the fallopian tubes, irritates the pelvic peritoneum, produces proliferation, and with an added unknown ingredient results in the development of ovarian cancer. If this is the case, ligation of the fallopian tubes may protect against ovarian cancer by means of preventing cancer-inducing agents from entering into the peritoneal cavity. The second hypothesis is that hormonal alteration after TS would make the risk of ovarian cancer lower. Preovulatory luteinising hormone (LH) peaks as well as midluteal LH levels were reported to significantly decline among women who experienced TS[76]. The reduced gonadotrophin levels have been suggested to be protective against ovarian cancer[77]. But, other research did not reveal a significant change in the level of either LH or follicular stimulating hormone (FSH) among tubo-sterilized women[78].

INDUCED ABORTION (IA) AND OVARIAN CANCER

As shown in the Table 2, 4 studies[22,30,34,51] reported the numbers of women who experienced IA among both cases and controls, though Harlow et al.[30] provided the numbers excluding nulligravid women. The test for combinability of the 4 ORs for induced abortion in these articles showed that these ORs were combinable (chi-square = 5.26, d.f. = 3, NS). As shown in Fig. 2, the summary OR for IA was 0.81 (95% CI 0.63-1.04, p = 0.093).

The purpose of IA may be different between the Asian countries and the Western countries in general. That is, IA has been common as a form of birth control in Asia where this method is ethically allowed. According to data from a nationwide survey for persons randomly sampled in Japan in 1989[79], about 80% of Japanese women indicated their willingness to undergo IA if necessary, and more than 40% of Japanese women aged 45-49 years had experienced IA. On the other hand, IA has been conducted in the Western countries primarily because of obstetrical reasons.

Consequently, it is worthwhile to analyze the data by strata, e.g. to analyze the data from the Asian countries only. The test for combinability of the 2 ORs in 2 case-control studies conducted in the Asian countries[34,51] concluded that these ORs were combinable (chi-square = 0.81, d.f. = 1, NS). The summary OR
Table 2. The published case-control studies on ovarian cancer which explained the number of women who underwent induced abortion.

<table>
<thead>
<tr>
<th>Reference no.</th>
<th>First author</th>
<th>Survey year</th>
<th>Survey area</th>
<th>No. of cases</th>
<th>Age restriction</th>
<th>Response rate for cases</th>
<th>No. of controls</th>
<th>Source of controls</th>
<th>Response rate for controls</th>
<th>Induced abortion</th>
<th>No. in cases</th>
<th>No. in controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>Tzonou</td>
<td>1980-1981</td>
<td>Athens</td>
<td>150</td>
<td>20-80 yrs.</td>
<td>68%</td>
<td>250</td>
<td>hospitals</td>
<td>74%</td>
<td>#</td>
<td>47</td>
<td>73</td>
</tr>
<tr>
<td>30</td>
<td>Harlow</td>
<td>1980-85</td>
<td>Washington</td>
<td>116</td>
<td>15-85 yrs.</td>
<td>99%</td>
<td>158</td>
<td>population</td>
<td>100%</td>
<td>#</td>
<td>172</td>
<td>114</td>
</tr>
<tr>
<td>34</td>
<td>Mori</td>
<td>1981-86</td>
<td>Japan</td>
<td>110</td>
<td></td>
<td></td>
<td>220 (110+110)</td>
<td>hospitals + screening</td>
<td>100%</td>
<td>#</td>
<td>41</td>
<td>50</td>
</tr>
<tr>
<td>51</td>
<td>Shu</td>
<td>1984-86</td>
<td>Shanghai</td>
<td>172</td>
<td>18-70 yrs.</td>
<td>100%</td>
<td></td>
<td>population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# : Exclude nulligravid women.

Figure 2. The summary odds ratio of ovarian cancer due to induced abortion. # : See Figure 1.

for IA in the Asian countries was 0.64 (95% CI 0.46-0.89, p<0.01).

Mori et al.31) showed that IA was inversely associated with the risk of ovarian cancer, even when adjusted for marital status, the number of livebirths, and TS (OR = 0.58, 95% CI 0.34-0.99). Prazzini et al.64) showed that the risk for ovarian tumor of borderline malignancy was significantly lower in women who experienced IA than in those who did not (OR = 0.2, 95% CI 0.1-0.6). However, this study was not involved in the present meta-analysis because of its small sample size. Negri et al.62) reported the result of a pooled analysis of 3 European case-control studies which showed an inverse association between abortion and the risk for ovarian cancer adjusted for parity and 5 other variables (OR for 2 or more abortions = 0.7, 95% CI 0.6-0.9). However, since they did not analyze the data by type of abortion, namely, induced or spontaneous, it was not clear whether this association was due to IA or not. Kvale et al.69) provided the result from a prospective cohort study of 60,565 women in Norway, of which 445 women were identified as having ovarian cancer during the follow-up from 1961 to 1980. The relative risk for ovarian cancer due to abortion, adjusted for the number of livebirths and demographic variables, was 0.89 (95% CI 0.69-1.16). However, this study also evaluated the combined effect of the two types of abortion. It seems premature to reach a conclusion regarding the relation between IA and ovarian cancer because of insufficient results obtained so far and because of the possibility of confounding by subfertility, similar to the case with TS.

**SUBFERTILITY AS A POTENTIAL CONFOUNDING FACTOR AND FURTHER EPIDEMIOLOGICAL STUDY ON OVARIAN CANCER**

There are numerous studies which have indicated the inverse association of oral contraceptives (OC) to the risk of ovarian cancer.4,5,7,8,12,14,18,22,26,30,40,41,54,55,60,63,72) Some of these studies showed that the association persisted even if the number of livebirths were
adjusted\textsuperscript{4,7,14,40,54,55,60,63}). Moreover, there are several reports of meta-analysis on association between OC and the risk for ovarian cancer\textsuperscript{80-82}. These of meta-analyses not only revealed statistically significant inverse associations of OC with the risk of ovarian cancer, but also showed that the relative risk was nearly as low for parous as for nulliparous women, and that greater declines in ovarian cancer risk were found with the longer periods of OC use. Two theories have been proposed to explain the relation between OC and ovarian cancer\textsuperscript{80,81}. The first one is that cessation in monthly ovulatory activity with OC decreases the risk. The second one is that suppression of the midcycle surge of pituitary gonadotrophins by OC reduces the risk.

However, there is a possibility that the inverse association between OC and ovarian cancer is an indirect one through subfertility because of the same relation as in the cases of TS or IA. Among various conditions which produce subfertility, premature ovarian failure has been suggested as most likely to be associated with the risk of ovarian cancer\textsuperscript{77}. Premature ovarian failure has been thought to increase the ovarian cancer risk through inducing excessive pituitary gonadotrophin stimulation to the ovaries\textsuperscript{77}. This is consistent with the result of a follow-up study of atomic-bomb survivors in Hiroshima and Nagasaki\textsuperscript{67}. That is, the high incidence rate of ovarian cancer was noted exclusively among women exposed to atomic-bomb radiation at the age of 20 years or younger, and it has been inferred from this result that radiation injury of ovaries at young ages and the subsequent excess of pituitary gonadotrophins may be important causative factors in the developments of ovarian cancer.

As stated by Johnson and Everitt\textsuperscript{83}, it would be generally accepted that in women having frequent, unprotected intercourse, failure to conceive within one year is worrying, and after 2 years of failure subfertility is clearly indicated. However, it is difficult to detect the presence of and to quantify the severity of subfertility\textsuperscript{84}. Parity may be a practical index of subfertility but may not be a complete one. Consequently, the following 4 questions should be included in further case-control studies on ovarian cancer to identify subfertility; (i) Have you ever failed to conceive for 2 years or longer in spite of unprotected intercourse with a partner?; (ii) If you are nulliparous, did you choose or did not choose to remain childless? (This sentence has been originally proposed by Weiss\textsuperscript{84}); (iii) If you are parous, have you practiced contraception after the last delivery?; (iv) If you had experienced induced abortion, what was the reason for doing so, i.e. having an obstetrical problem or as a form of birth control? Further, a more detailed questionnaire regarding menstrual disorders such as amenorrhea and irregularity before or during the reproductive ages, early menopause, TS, IA, OC, and other birth-control methods need to be applied to evaluate subfertility. When the association of TS, IA, or OC with ovarian cancer is evaluated, the magnitude of correlation among these birth-control methods should be quantified.

Variables concerning physiological, chemical, or biological exposures such as frequent diagnostic irradiations to abdomen, environmental tobacco smoke, and infection of mumps virus, which have been postulated as the causes of premature ovarian failure\textsuperscript{85}, should also be included in case-control studies on ovarian cancer. Further, it would be preferable for the cases to be stratified by degree of malignancy of ovarian tumor, although some risk factors seem to be common between ovarian carcinomas and tumors of borderline malignancy\textsuperscript{20,43,64}.

There is a possibility that hospital controls may offer estimates biased from a general population with regard to the proportion of such variables as TS, IA, and OC. For example, as shown in Tables 1 and 2, half of the cited case-control studies\textsuperscript{22,34,39,41} utilized medical institutions as a source of controls, and the residual half\textsuperscript{32,51,58} used population controls. Calculated from the numbers on Tables 1 and 2, the pooled percentage of TS among the hospital controls (13.3%) was slightly lower than that among the population controls (17.0%), and conversely, that of IA among the hospital controls (50.5%) was higher than among the population controls (35.5%). Thus, it is recommended to select the controls from a general population rather than from a medical institute, especially when the associations of the birth-control methods with ovarian cancer would be assessed.

As mentioned by Fleiss and Gross\textsuperscript{73}, publication bias is one of the essential problems in the meta-analysis, when only published data are available, because articles that fail to show an effect are often rejected for publication, or there is a tendency on the authors' part not to submit for publication an article that fails to show an effect. However, because the association of TS with ovarian cancer was recently initially hypothesized\textsuperscript{75}, an article which did not indicate a significant finding on this association might less likely have been rejected for publication as compared to a nonsignificant finding on the well-established risk factors. Furthermore, since 5 among 6 published reports (83.3%) showed that there was a significantly inverse relationship of TS to ovarian cancer, authors who obtained a nonsignificant finding on this relation may have wanted to publish their findings because of an unique result. Consequently, publication bias less
likely be present in our meta-analysis of tubal sterilization and probably induced abortion with ovarian cancer.

ACKNOWLEDGMENTS

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75. Woodruff JD. The pathogenesis of ovarian neoplasia, Johns Hopkins Med J, 1979; 144: 117-120.