Reproductive Factors and Risk of Cancer of the Uterine Corpus: A Prospective Study

Gunnar Kvåle, Ivar Heuch, and Giske Ursin

Department of Hygiene and Social Medicine [G. K., G. U.], and Department of Mathematics [I. H.], The University of Bergen, Norway

ABSTRACT

Relationships between reproductive factors and risk of cancer of the uterine corpus were investigated in a prospective study of 62,079 women in Norway. A total of 420 cases were diagnosed during follow-up, from 1961 through 1980. The risk of endometrial carcinoma decreased significantly with increasing parity as well as with increasing age at first and last birth. The estimated odds ratio for women with 5 or more births versus uniparous was 0.60 in analyses with adjustment for age and residence characteristics. For first birth at age $\geq 35$ versus $\leq 19$ the odds ratio was 0.48, and for last birth at age $\geq 40$ versus $\leq 24$ we found an odds ratio of 0.45, in analyses with additional adjustment for parity. Significant associations were also found with age at menarche and menopause, the highest risks being observed for women with early menarche or late menopause. The different reproductive variables seemed to affect the risk of sarcomas of the uterine corpus and the risk of endometrial carcinomas in a similar way.

INTRODUCTION

Relationships between reproductive factors and endometrial carcinoma have been examined in a number of studies, mainly by the case-control approach. Most reports have agreed on an inverse association with parity and a positive association with age at menopause, whereas findings regarding effects of age at first birth and age at menarche have been less clear (1). In the present report these relationships are assessed on the basis of a prospective population-based study of 62,079 women with detailed information on reproductive variables obtained through personal interviews. Previous reports from this cohort have dealt with risk of cancer of the breast (2-4) and the ovaries (5).

MATERIALS AND METHODS

In 1956-1959, all women aged 20-69 years by January 1, 1956, in four counties in Norway were invited to attend a screening program for early diagnosis of breast cancer. Each woman was interviewed according to a standard questionnaire and had a clinical breast examination carried out by a physician. In addition to demographic data, the questionnaire elicited information on different reproductive variables; age at menarche and menopause, number of full-term deliveries, age at first and last birth, number of abortions, and duration of lactation. The present study is confined to residents of the three counties Vestfold, Aust-Agder, and Nord-Trøndelag, aged 27-69 years by January 1, 1956, totaling 92,573 women. The official personal registration number was retrieved for 85,063 women who were still alive at start of follow-up on January 1, 1961. Of these, 63,090 had attended the screening program and were interviewed during the years 1956-1959, corresponding to a response rate of 74.2% in this group. After exclusion of 1,011 participants who reported surgical removal of the uterus or therapeutic radiation of the genital organs, 62,079 women remained for follow-up. The official registration number served as a unique identification of the record for each woman and was used to link follow-up information to our files. Thus, data on cancer cases, obtained from the Cancer Registry of Norway, and complete information concerning emigrations and deaths, from the Central Bureau of Statistics, could be added to the records with information on reproductive and other variables. Dates of diagnosis and sites of primary tumor were thoroughly checked by the Cancer Registry, and this information as well as histological subtype recorded, was not revised for this study. The Cancer Registry covers the whole population of Norway, and the registration is practically complete for all sites, including cancer of the corpus uteri (6). Data on height and weight were linked to our files for 63,086 women who also attended a screening program organized by the National Mass Radiography Service in the period 1963-1975.

All cases classed as primary malignant neoplasms of the uterine corpus (ICD 7th Revision 172) were considered. A total of 420 cases were diagnosed in the cohort during follow-up. Of these, 419 were histologically verified, and 382 were classified as endometrial carcinomas (364 adenocarcinomas, seven adenosquamous carcinomas, eight other carcinomas), and 29 as sarcomas (14 leiomyosarcomas, three Stromal sarcomas, three mixed mesodermal sarcomas, nine other sarcomas). The remaining histologically verified cases were six carcinosarcomas, one case of mesonephroma, and one case with an aplastic tumor, not otherwise specified.

Separate statistical analyses were carried out for the two main subsets of histologically confirmed cases, the endometrial carcinomas and the sarcomas. The analyses were adjusted for age at start of follow-up (with 5-year age groups) and urban/rural place of residence, and in special situations other demographic and reproductive variables. The adjustment was made by forming a stratum for each combination of categories for the covariables. On the basis of the total number of cases included in any particular analysis, the expected number was found for each level of the study variable, assuming no association with cancer (7). Of the 62,079 participants, 13,828 died and 124 emigrated in the period 1961-1980. Times of death and emigration were taken into account in the calculation of expected numbers (8). These numbers were also utilized in tests for trend in association with cancer, performed by the stratified extension of the Cochran-Armitage statistic (9). Tests for departure from a linear trend allowed assessment of the appropriateness of the model.

Odds ratios were estimated by stratified logistic regression analysis (7). In the estimation procedure, a correction for censoring was introduced by diminishing the initial number at risk by half the number of deaths and emigrations occurring among those who did not develop the cancer in question. Separate tests were carried out for interaction between the study variable and the particular variables defining strata. Because of missing values and exclusion of uninformative strata, the number of women included was not the same in all analyses.

RESULTS

The risk of endometrial carcinoma decreased with increasing parity (Table 1). This statistically significant inverse association was strengthened by adjustment for age at first birth. We observed no definite trend according to the number of abortions. In parous women the odds ratio for those with $\geq 3$ abortions versus women not reporting any abortion was 1.03 (95% confidence interval, 0.58-1.82) in logistic regression analysis with adjustment for parity and age at first birth in addition to demographic variables. In the group of nulliparous women, ever-married had somewhat lower risk estimate than never-married women (odds ratio, 0.79; 95% confidence interval,
Table 1  Endometrial carcinoma by parity

<table>
<thead>
<tr>
<th>Parity Score</th>
<th>Total series with known parity, adjusted for age and urban/rural place of residence</th>
<th>Parous women, also adjusted for age at first birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>O/E</td>
<td>O/E</td>
</tr>
<tr>
<td>0</td>
<td>93</td>
<td>68</td>
</tr>
<tr>
<td>1</td>
<td>69</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>99</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>20</td>
</tr>
<tr>
<td>≥5</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>371</td>
<td>264</td>
</tr>
</tbody>
</table>

R* (With 95% conf. int.)

0.60*** (0.40–0.89)

Relative odds estimate, parous with five or more births versus uniparous based on logistic regression analysis with five levels of parity.

Two-tailed P values for trend: **. 0.001 < P ≤ 0.01; ***. P ≤ 0.001.

0.52–1.20). Among parous ever-married women we observed no notable association between risk and duration between marriage and first birth, in analyses adjusted for parity and age at first birth (odds ratio for duration ≥3 years versus <1 year, 1.08; 95% confidence interval, 0.67–1.74).

The risk decreased with increasing age at first and last births in analyses with adjustment for parity (Tables 2 and 3). Parity, age at first and age at last birth were strongly correlated, and in analyses for one particular variable with adjustment for all the others, the inverse associations were weakened. The associations with parity and age at first and last birth still obtained after additional adjustment for age at menarche or menopause.

Age at menarche was inversely and age at menopause positively associated with the risk of endometrial carcinoma in analyses with adjustment for demographic characteristics and parity (Table 4). Additional adjustment for age at first and last birth hardly affected these risk estimates. The relative odds estimate for women reporting irregular menstruation versus other women was 0.85 in analyses with adjustment for parity and age at menarche (95% confidence interval, 0.54–1.35).

The association with age at menopause was weak for cancers diagnosed late in life (Table 5), whereas no heterogeneity in effects according to age at diagnosis could be observed for age at menarche, parity or age at first and last births. The associations with the reproductive variables were consistently found in all subgroups of the material according to county and urban/rural place of residence. Relationships with parity and age at first and last birth were not notably weakened after additional adjustment for occupational class, or body mass index (weight/height²), a strong risk factor for endometrial carcinoma in this cohort. Potential confounding with body mass index could only be assessed for cases diagnosed in the later part of the follow-up period in a subgroup of the cohort. In this group associations with age at menopause and age at menarche were weakened after adjustment for body mass index. For age at menarche we observed a possible interaction with body mass index. In women with body mass index ≤25 kg/m² late menarche was protective, whereas among more obese women with very late menarche (≥17 years) an increased risk was observed.

Like endometrial carcinomas, sarcomas of the uterine corpus showed inverse relationships with parity, age at first and last birth and age at menarche, and a positive relationship with age

Table 2  Endometrial carcinoma by age at first birth

<table>
<thead>
<tr>
<th>Age at first birth (years)</th>
<th>O</th>
<th>O/E</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤19</td>
<td>13</td>
<td>1.14</td>
<td>264</td>
</tr>
<tr>
<td>20–24</td>
<td>100</td>
<td>1.17</td>
<td>196</td>
</tr>
<tr>
<td>25–29</td>
<td>98</td>
<td>1.04</td>
<td>196</td>
</tr>
<tr>
<td>30–34</td>
<td>32</td>
<td>0.65</td>
<td>196</td>
</tr>
<tr>
<td>≥35</td>
<td>21</td>
<td>0.92</td>
<td>196</td>
</tr>
</tbody>
</table>

R* (With 95% conf. int.)

0.48*** (0.28–0.83)

Relative odds estimate, parous with age at first birth ≥35 versus <19 years based on logistic regression analysis with five levels of age at first birth.

Two-tailed P value for trend: **. 0.001 < P ≤ 0.01.

0.52–1.20). Among parous ever-married women we observed no notable association between risk and duration between marriage and first birth, in analyses adjusted for parity and age at first birth (odds ratio for duration ≥3 years versus <1 year, 1.08; 95% confidence interval, 0.67–1.74).

The risk decreased with increasing age at first and last births in analyses with adjustment for parity (Tables 2 and 3). Parity, age at first and age at last birth were strongly correlated, and in analyses for one particular variable with adjustment for all the others, the inverse associations were weakened. The associations with parity and age at first and last birth still obtained after additional adjustment for age at menarche or menopause.

Age at menarche was inversely and age at menopause positively associated with the risk of endometrial carcinoma in analyses with adjustment for demographic characteristics and parity (Table 4). Additional adjustment for age at first and last birth hardly affected these risk estimates. The relative odds estimate for women reporting irregular menstruation versus other women was 0.85 in analyses with adjustment for parity and age at menarche (95% confidence interval, 0.54–1.35).

The association with age at menopause was weak for cancers diagnosed late in life (Table 5), whereas no heterogeneity in effects according to age at diagnosis could be observed for age at menarche, parity or age at first and last births. The associations with the reproductive variables were consistently found in all subgroups of the material according to county and urban/rural place of residence. Relationships with parity and age at first and last birth were not notably weakened after additional adjustment for occupational class, or body mass index (weight/height²), a strong risk factor for endometrial carcinoma in this cohort. Potential confounding with body mass index could only be assessed for cases diagnosed in the later part of the follow-up period in a subgroup of the cohort. In this group associations with age at menopause and age at menarche were weakened after adjustment for body mass index. For age at menarche we observed a possible interaction with body mass index. In women with body mass index ≤25 kg/m² late menarche was protective, whereas among more obese women with very late menarche (≥17 years) an increased risk was observed.

Like endometrial carcinomas, sarcomas of the uterine corpus showed inverse relationships with parity, age at first and last birth and age at menarche, and a positive relationship with age

Table 3  Endometrial carcinoma by age at last birth

<table>
<thead>
<tr>
<th>Age at last birth (years)</th>
<th>O</th>
<th>O/E</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤24</td>
<td>22</td>
<td>1.04</td>
<td>264</td>
</tr>
<tr>
<td>25–29</td>
<td>84</td>
<td>1.35</td>
<td>196</td>
</tr>
<tr>
<td>30–34</td>
<td>75</td>
<td>0.90</td>
<td>196</td>
</tr>
<tr>
<td>35–39</td>
<td>62</td>
<td>0.92</td>
<td>196</td>
</tr>
<tr>
<td>≥40</td>
<td>62</td>
<td>0.70</td>
<td>196</td>
</tr>
</tbody>
</table>

R* (With 95% conf. int.)

0.45*** (0.27–0.75)

Relative odds estimate, parous with age at last birth ≥40 versus <24 years based on logistic regression analysis with five levels of age at last birth.

Two-tailed P value for trend: **. 0.001 < P ≤ 0.01.
The most important reproductive risk factors for endometrial cancer identified to date include infertility, low parity, late menopause, and possibly early age at menarche (1). In agreement with many reports we found high risk among nulliparous women (21–34), and a decrease in risk with an increasing number of childbirths after the first birth (22–23, 26, 29–30, 33–37). Only few studies have found no such decrease (32, 38–39). Incomplete pregnancies showed no notable association with risk of endometrial carcinoma in our cohort, whereas previous results have not been consistent (26, 37).

### DISCUSSION

Our results indicate that low parity, low age at first and last birth, early menarche, and late menopause are related to an increased risk of endometrial carcinoma, whereas no association with duration of lactation was found after adjustment for parity (4). These results are based on follow-up of a cohort recruited among participants in a screening program for breast cancer. The participation rate was generally high (74.2%), but showed some variation according to age and residence (2). Standard adjustment for these variables served to reduce confounding as well as to minimize possible bias related to selective attendance. Such bias can occur only if participation rates for cases and noncases are differentially affected by the risk factor studied (10). The 20-year follow-up of our cohort started 1–5 years after the screening examination, and only cases diagnosed in this period were considered. Symptoms of uterine cancer should hardly influence participation in a screening program for breast cancer several years before diagnosis.

We had no individual information on use of oral contraceptives, estrogen replacement therapy, or smoking. Oral contraceptives were introduced in Norway in 1967 when the youngest women in our cohort were 38 years of age, and 80.7% of the participants were 45 years or more. As late as in 1983 oral contraceptives were only used by approximately 20% of Norwegian women aged 18–44 years (11), and estrogen replacement therapy by about 9% of the women aged 45–54 (12). It thus seems unlikely that exogenous hormones should notably affect relationships in our cohort between other variables and risk of cancer of the uterine corpus.

Several studies have shown that cigarette smoking is related to low risk of endometrial cancer (13–19) and to early menopause (13). However, the prevalence of smoking in our cohort, consisting mainly of women in rural areas, was probably less than that observed in a national survey in 1964. The proportion of current smokers was then found to vary from about 40% among women aged 30–34 years to about 10% among those aged 65 or more (20). The associations with reproductive variables described here showed no systematic variation over age groups and still obtained in analyses restricted to rural residents only. This indicates that confounding with smoking should not markedly influence these associations.

### Table 5 Endometrial carcinoma and reproductive variables

<table>
<thead>
<tr>
<th>Reproductive variable</th>
<th>Parity</th>
<th>Age at first birth</th>
<th>Age at last birth</th>
<th>Age at menarche</th>
<th>Age at menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categories compared</td>
<td>≥5 births vs. nulliparous</td>
<td>≥35 yr. vs. &lt;19 years</td>
<td>≥40 yr. vs. ≥24 years</td>
<td>≥17 yr. vs. ≤12 years</td>
<td>≥54 yr. vs. ≥45 years</td>
</tr>
<tr>
<td>Total series</td>
<td>O</td>
<td>R²</td>
<td>O</td>
<td>R²</td>
<td>O</td>
</tr>
<tr>
<td>Age at diagnosis (yr.)</td>
<td>O</td>
<td>R²</td>
<td>O</td>
<td>R²</td>
<td>O</td>
</tr>
<tr>
<td>&lt;50</td>
<td>33</td>
<td>0.54</td>
<td>21</td>
<td>0.16</td>
<td>11</td>
</tr>
<tr>
<td>50–59</td>
<td>145</td>
<td>0.37</td>
<td>106</td>
<td>0.82</td>
<td>106</td>
</tr>
<tr>
<td>60–69</td>
<td>121</td>
<td>0.49</td>
<td>89</td>
<td>0.36</td>
<td>89</td>
</tr>
<tr>
<td>≥70</td>
<td>72</td>
<td>0.61</td>
<td>48</td>
<td>0.49</td>
<td>48</td>
</tr>
</tbody>
</table>

* Relative odds estimates (R²) based on logistic regression analyses with five levels of age at first or last birth, adjusted for age, urban/rural place of residence and parity.

** Two-tailed P values: *, 0.01 < P ≤ 0.05; **, 0.001 < P ≤ 0.01; ***, P ≤ 0.001.
Table 6  Sarcoma of the corpus uteri by reproductive variables

<table>
<thead>
<tr>
<th>Categories compared</th>
<th>Number of cases</th>
<th>Relative odds estimate</th>
<th>(95% conf. int.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parous vs. nulliparous*</td>
<td>27</td>
<td>1.27</td>
<td>(0.43-3.68)</td>
</tr>
<tr>
<td>Parity ≥5 vs. parity 1*</td>
<td>20</td>
<td>0.06***</td>
<td>(0.01-0.44)</td>
</tr>
<tr>
<td>Age at first birth:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first birth ≥35 vs. ≤19 years*</td>
<td>20</td>
<td>0.34</td>
<td>(0.05-2.19)</td>
</tr>
<tr>
<td>Age at last birth (years):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at last birth ≥40 vs. ≤24 years*</td>
<td>20</td>
<td>0.23</td>
<td>(0.04-1.40)</td>
</tr>
<tr>
<td>Age at menarche (years):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at menarche ≥17 vs. ≤12 years*</td>
<td>27</td>
<td>0.52</td>
<td>(0.12-2.34)</td>
</tr>
<tr>
<td>Age at menopause:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at menopause ≥54 vs. ≤45 years*</td>
<td>7</td>
<td>6.23</td>
<td>(0.41-94.0)</td>
</tr>
</tbody>
</table>

* Adjusted for age at start of follow-up and urban-rural place of residence.

The strong and highly significant inverse associations observed with age at first and last birth were not expected since most previous studies have shown no such relation either with age at first (22, 26, 29-30, 32, 37, 39) or last (37, 39) birth. However, Pettersson et al. (33) found a statistically significant lower age at last birth among patients with endometrial carcinoma than among controls, and a smaller but not significant difference in age at first birth.

A possible explanation for these divergent findings may relate to the study design. Whereas our study is prospective, all former studies were of the case-control type, and several used hospitalized patients (22, 30, 32, 39) or other cancer patients (29) as controls. The study that did show associations with age at first and last birth similar to those seen by us (33), used controls selected from the general population. In our cohort, early age at first birth was associated with high mortality for cardiovascular and other common noncancer causes of death. Thus, in a case-control study recruiting controls among patients with other diseases, an increased risk among women with early first birth may easily be masked if patients with other diseases belong to subgroups of the population with early first birth.

Moreover, several previous studies have not presented results adjusted for parity (22, 32-33, 39). We observed evidence of the expected negative confounding by parity in the relationship with age at first birth; the inverse association became stronger and reached statistical significance only after adjustment for parity. It is difficult in our data to separate completely the effects of age at first and last birth, but our results suggest that the age at every pregnancy may have an independent effect.

The protective effect of a pregnancy may be explained by hormonal effects (37). However, the low risk observed among women with late births, contrasting with results for breast cancer (3), suggests that nonsystemic risk factors related to reproduction may also play an essential part.

Our results regarding the effect of age at menopause are consistent with a number of studies showing a positive association, as reviewed by Kelsey and Hildreth (1). In agreement with the findings of Pettersson et al. (33), we observed a strong effect of late menopause for cancers occurring before the age of 70, and only a relatively weak association in higher age groups.

Previous studies regarding the effect of age at menarche have been equivocal (1), with some studies showing no definite relationship (33, 37). However, our results support several studies indicating that late menarche in general is protective (26, 30, 32, 38). In analyses involving the 212 cases with measurements of height and weight before the cancer was diagnosed, we observed indications of an interaction with body mass index. In obese women menarche after the age of 16 years was associated with increased risk. Henderson et al. (37) also described contradictory results in different weight categories, but in contrast to our results, they found that relative to the controls, the obese cases tended to have early menarche.

Our relative odds estimates based on the total series imply an increase in risk per year decrease in age at menarche equal to 11.4% (95% confidence interval, 2.7–20.8%). The corresponding increase in risk per year increase in age at menopause was 9.8% (95% confidence interval, 2.3–17.9%). These associations are considerably stronger than those observed for breast cancer in our cohort.3 On the basis of the shape of the age incidence curve for endometrial cancer, an effect of age at menopause would be expected of the magnitude seen here (40). Similarly, an effect of age at menarche as observed by us would be anticipated if menarche is the main determinant of the age when the steep increase in incidence starts.

It has been suggested that the “unopposed estrogen” hypothesis (40, 41) can account for relationships with several risk factors for endometrial carcinoma, e.g., obesity, smoking and estrogen replacement therapy (40). This hypothesis can explain observed associations in young women between endometrial cancer and the Stein-Leventhal syndrome (1) as well as other conditions involving infertility (37, 42). It might also imply high risk in older women reporting previous fertility problems. We found, however, that ever-married nulliparous women had somewhat lower risk than never-married nulliparous. Other studies mainly involving old cases have shown no difference (21) or only moderately increased risk among ever-married nulliparous women (26, 30). This suggests that the effect of infertility on the incidence of endometrial cancer in a population of older women is likely to be small. Our results showing no increased risk in women with irregular cycles or long duration between marriage and first birth are consistent with this conclusion.

We found no difference in the effects of reproductive factors according to histological type. We are not aware of other studies that have examined the effect of reproductive factors on the incidence of sarcomas of the uterus. Considering the age-incidence pattern for leiomyosarcomas of the uterus, Harlow et al. (43) suggested that factors which play a role in the etiology of carcinomas of the reproductive tract may be involved in the etiology of the leiomyosarcomas as well. Our results are consistent with this hypothesis. Of the 29 uterine sarcomas, 14 were classified as leiomyosarcomas. The numbers were too small for meaningful separate analyses of the different types of sarcomas. However, we observed no notable difference in effects of reproductive variables between leiomyosarcomas and the group of other and unspecified sarcomas of the uterus. The 45 nonuterine sarcomas diagnosed in our cohort were not strongly associated with any of the reproductive variables examined here.

ACKNOWLEDGMENTS

The authors acknowledge the work of numerous physicians and public health nurses who conducted the interviews, and the work of the

2 G. Kvåle and I. Heuch, Menstrual factors and breast cancer risk, submitted for publication.
The authors also thank Aage Andersen, Geir Egil Eide, and Steinar Nilsen for assistance in the data processing. The data on height and weight were provided by the National Health Screening Surveys.

REFERENCES

Reproductive Factors and Risk of Cancer of the Uterine Corpus: A Prospective Study

Gunnar Kvåle, Ivar Heuch and Giske Ursin


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/48/21/6217

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.