Marianne Hinkula

INCIDENCE OF GYNAECOLOGICAL CANCERS AND OVERALL AND CAUSE SPECIFIC MORTALITY OF GRAND MULTIPAROUS WOMEN IN FINLAND
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INCIDENCE OF GYNAECOLOGICAL CANCERS AND OVERALL AND CAUSE SPECIFIC MORTALITY OF GRAND MULTIPAROUS WOMEN IN FINLAND

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**Abstract**

The aim of this population-based cohort study was to evaluate the incidence and relative risk ratios of gynaecological cancers and the mortality of women with at least five children (GM women) compared to the average of Finnish women. We linked together the data of the Population Register (1974–1997), the Finnish Cancer Registry and the national cause-of-death files of Statistics Finland (1974–2001) by using a personal identification code. The study population consisted of 86 978 GM women (1974–1997), including 3 752 women with at least 10 children (GGM women). Altogether 7 604 cancer diagnoses and 18 870 deaths were recorded.

The incidence (SIR) of breast (0.55, 95% CI 0.52–0.58), endometrial (0.57, 95% CI 0.52–0.63) and ovarian cancer (0.64, 95% CI 0.55–0.73) decreased, and that of cervical cancer (1.13, 95% CI 0.98–1.29) increased in GM women. In multivariate analysis, the increase in parity from five to eight increased the protection against breast and endometrial cancer, but not in ovarian or cervical cancer. A young age at first birth decreased the breast cancer risk, while an older age at first birth decreased the risk for endometrial and cervical cancer. A short premenopausal delivery-free period and a long birth period were risk reducers in women who contracted endometrial cancer after menopause.

The mortality (SMR) of breast (0.64, 95% CI 0.59–0.69), endometrial (0.68, 95% CI 0.56–0.80), ovarian cancer (0.68, 95% CI 0.60–0.75) as well as for dementia (0.80, 95% CI 0.72–0.84) decreased. The SMR of kidney (1.38, 95% CI 1.21–1.56) cancer increased in the GM group. The SMR of ischemic heart diseases (1.10, 95% CI 1.08–1.13) and diabetes mellitus (1.42, 95% CI 1.29–1.55) increased. The overall SMR of GM women was 5% less than expected (95% CI 0.94–0.95; deficit 949 deaths), but among GGM women it coincided with the national average (1.01, 95% CI 0.93–1.08).

Multiparity affected the spectrum of diseases and causes of death in a specific way: the pregnancy-specific hormonal milieu is responsible for the low SIR and SMR of hormone-dependent cancers, and increased body weight is lightly responsible for the high SMR of cardiovascular and metabolic diseases. These observations advocate for delivering the first child at an age younger than 30 years and to start measures for careful weight control not only during and after pregnancies but even later and permanently.

**Keywords:** breast neoplasms, cervix neoplasms, endometrial neoplasms, incidence, mortality, ovarian neoplasms, parity
"The immunity even increases with the density of the family that is with the increase in the number of its elements.” Durkheim stated the importance of family size over 100 years ago.

To Pekka and Annukka
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Oulu, January, 2006

Marianne Hinkula
Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BRCA</td>
<td>Breast cancer antigen</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>CIS</td>
<td>Cervical cancer in situ</td>
</tr>
<tr>
<td>C. trachomatis</td>
<td>Chlamydia trachomatis</td>
</tr>
<tr>
<td>ER</td>
<td>Oestrogen receptor</td>
</tr>
<tr>
<td>FMC</td>
<td>Finnish Maternity Cohort</td>
</tr>
<tr>
<td>FSH</td>
<td>Follicle stimulating hormone</td>
</tr>
<tr>
<td>GGM</td>
<td>Grand grand multiparity</td>
</tr>
<tr>
<td>GM</td>
<td>Grand multiparity</td>
</tr>
<tr>
<td>GnRh</td>
<td>Gonadotropin releasing hormone</td>
</tr>
<tr>
<td>hCG</td>
<td>Human chorionic gonadotropin</td>
</tr>
<tr>
<td>HDL</td>
<td>High density lipoprotein</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HPL</td>
<td>Human placental lactogen</td>
</tr>
<tr>
<td>HPV</td>
<td>Human papilloma virus</td>
</tr>
<tr>
<td>HRT</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>HSIL</td>
<td>High squamous intraepithelial lesion</td>
</tr>
<tr>
<td>IGF</td>
<td>Insulin-like growth factor</td>
</tr>
<tr>
<td>IUCD</td>
<td>Intra uterine contraceptive device</td>
</tr>
<tr>
<td>LH</td>
<td>Luteinizing hormone</td>
</tr>
<tr>
<td>LSIL</td>
<td>Low squamous intraepithelial lesion</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PR</td>
<td>Progestin receptor</td>
</tr>
<tr>
<td>RR</td>
<td>Risk ratio</td>
</tr>
<tr>
<td>SCC</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>SIR</td>
<td>Standardised incidence ratio</td>
</tr>
<tr>
<td>SMR</td>
<td>Standardised mortality ratio</td>
</tr>
<tr>
<td>STI</td>
<td>Sexually transmitted infection</td>
</tr>
</tbody>
</table>
List of original publications

This thesis is based on the following articles, which are referred to in the text by their Roman numerals:


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1 Introduction

Hormones play a major role in the aetiology of several cancers of women, including cancers of the breast, endometrium and ovary. Hormones affect the cancer risk e.g. by controlling the rate of cell division, the differentiation of cells and the number of susceptible cells. Oestrogens stimulate mitosis in the endometrium, whereas progesterin opposes this phenomenon. Both oestrogens and progestins stimulate mitosis in the breast. Hormones do not have any marked direct effects on the epithelial cells covering the ovaries. However, they stimulate ovulation, which is followed by follicular epithelial rupture and consequent cell division during the repair of the epithelium. The lifetime number of ovulations may be a determinant for ovarian cancer risk. In breast, endometrial and ovarian cancer, the risk changes in line with varying exposure to sex hormones. Some of the changes in the risk persist for many years, indicating that hormones can affect both early and late stages of carcinogenesis. (Key 1995.)

Parity is consistently protective for all hormone dependent gynaecological cancers, and the extent of such a protection varies with age at pregnancy. The effect of parity on the development of gynaecological cancers has been widely evaluated for up to five births. (MacMahon 1974, La Vecchia et al. 1989, Lambe et al. 1999, Riman et al. 2004.) The RR of nulliparous women to contract breast cancer ranges from 1.2 to 1.7 in comparison with parous women (Kelsey et al. 1993b). The protection rate increases with increasing parity (La Vecchia et al. 1989). Early age at first full term pregnancy decreases the risk of breast cancer (La Vecchia et al. 1989, Kelsey & Whittemore 1994), whereas late age at first delivery seems to protect against endometrial cancer (Lesko et al. 1991, Brinton et al. 1992, Lambe et al. 1999). In ovarian cancer, each full-term pregnancy will offer a 15-20% reduction in risk (Adami et al. 1994), but the age at first birth has no effect on the risk (Adami et al. 1994, Kelsey & Whittemore 1994, Riman et al. 2004). Increases in the number of births and young age at first birth are associated with an increased risk of cervical cancer, even though the actual aetiological factors are human papillomaviruses rather than hormones (Walboomers et al. 1999, Muñoz et al. 2002). Previous studies on the association between reproductive factors and gynaecological cancers often suffer from lack of validity because of the small number of subjects involved (Franceschi 1989).
The mortality of GM women (= women with at least five children) has been examined in some studies but never comprehensively (Beral 1985, Green et al. 1988, Kvåle et al. 1994, Grundy & Tomassini 2005). The parous women had a lower mortality of breast, ovarian and endometrial cancer than nulliparous women, but they had a higher mortality from diabetes mellitus, gallbladder diseases, cervical cancer, nephritis and nephrosis, hypertension, ischemic and degenerative heart disease, cerebrovascular diseases and all causes of death (Beral 1985, Kvåle et al. 1994). In the study by Green et al. (1988), including all causes of death for nulliparous women, the SMR (= standardised mortality rate) was 113 for nulliparous married women, which was significantly higher (p < 0.01) than the SMR 97 for parous married women. In another English study, nulliparous women and GM women had a significantly higher mortality than other women (Grundy & Tomassini 2005). There may be residual and cumulative effects of childbearing on the patterns of disease, which manifest themselves after the reproductive years (Green et al. 1988).

Our study based on a national cohort of GM women was conducted to elucidate the incidence (SIR) and independent relative risk ratios (RR) of parity and some other reproductive factors in gynaecological cancers, and the overall and cause specific SMR in those gynaecological such as breast, endometrium, ovarian and cervical cancer, as well as other diseases of GM women. The Population Registry of Finland (Statistics Finland) has recorded information about all families and children since 1974. The Finnish Cancer Registry includes information about the diagnosis, clinical stage and clinical course of cancers since 1967 (Teppo et al. 1994). The reliability of the causes of deaths in the national cause-of-death files is deemed to be adequate for the SMR calculations in different causes of death (Heliövaara et al. 1984, Stenbäck 1986), and since 1936 the statistics concerning death have been based on death certificates written by medical doctors (Statistics Finland 2004). In this study we linked together the data on Finnish women from three sources to find out about the effects of childbearing of GM women on gynaecological cancer risk and mortality.
2 Review of the literature

2.1 Definitions and pregnancy outcome of GM women

The term grand multipara (GMP), introduced in 1934 by Solomons (Solomons 1934), describes a woman who has undergone five or more deliveries. Women who have undergone at least ten deliveries are called grand grand multiparas (GGMP), as introduced by Silva (Silva 1992). During the last few decades, the proportion of GMPs has decreased in most developed countries because of a dramatic change in the practice of contraception. The proportion of GM women in our country was 2.3% (n=1342) in 1997 and 2.6% (n=1416) in 2002 (Stakes 2002).

In the retrospective review of history of pregnancies and births of 96 GGMP parturient individuals treated in the Oulu University Hospital, in Oulu, Finland during 1989–1990, the highest number of deliveries/woman was 25, and the mean interval between consequent births was 8.5 ± 5.6 months after a delivery and 5.3 ± 4.8 months after an abortion (deliveries of twins and premature births had no effect on the interpregnancy intervals) (Juntunen et al. 1994). In this study, the GGMP women had an increased risk of hypertensive and diabetic complications, but nevertheless, the perinatal results remained quite similar and good from the first to the last pregnancies and deliveries, possibly owing to good maternal health care system in Finland. (Table 1) (Juntunen et al. 1997.)
Table 1. Total number of deliveries, mean age, weight and BMI and frequency (%) of different complications of pregnancy and delivery and neonatal observation in relation to four birth order groups of 96 GGM women (Juntunen et al. 1997).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1 (96)</th>
<th>2-5 (384)</th>
<th>6-9 (384)</th>
<th>10-20 (336)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical observations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age of mother (years)</td>
<td>22±2.3</td>
<td>25.4±2.8</td>
<td>31.3±3.1</td>
<td>37.9±3.3</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>59±8</td>
<td>61±10</td>
<td>66±11</td>
<td>71±12</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>22±2.7</td>
<td>23±4.1</td>
<td>25±3.8</td>
<td>27±4.4</td>
</tr>
<tr>
<td>Pregnancy complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-eclampsia, %</td>
<td>13.5</td>
<td>2.1</td>
<td>1.8</td>
<td>3.0</td>
</tr>
<tr>
<td>Hypertension gravidarum, %</td>
<td>0.0</td>
<td>6.8</td>
<td>6.3</td>
<td>8.0</td>
</tr>
<tr>
<td>Hypertension essentialis, %</td>
<td>0.0</td>
<td>2.1</td>
<td>6.0</td>
<td>7.4</td>
</tr>
<tr>
<td>Diabetes gestationalis, %</td>
<td>0.0</td>
<td>0.0</td>
<td>2.7</td>
<td>6.0</td>
</tr>
<tr>
<td>Delivery complications</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Preterm delivery &lt; 37 weeks, %</td>
<td>2.1</td>
<td>4.4</td>
<td>6.3</td>
<td>4.8</td>
</tr>
<tr>
<td>Induced delivery, %</td>
<td>22.3</td>
<td>16.8</td>
<td>22.7</td>
<td>33.3</td>
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<tr>
<td>Caesarean section, %</td>
<td>1.1</td>
<td>1.2</td>
<td>2.3</td>
<td>7.1</td>
</tr>
<tr>
<td>Neonatal observations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small for gestational age, %</td>
<td>11.7</td>
<td>4.8</td>
<td>3.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Large for gestational age, %</td>
<td>7.4</td>
<td>8.3</td>
<td>17.8</td>
<td>22.6</td>
</tr>
<tr>
<td>Congenital anomalies, %</td>
<td>1.1</td>
<td>0.3</td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Chromosomal anomalies, n</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Perinatal mortality, %</td>
<td>1.1</td>
<td>2.1</td>
<td>2.1</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Some studies have shown that GM women carry great obstetrical risks (Fuchs et al. 1985, Abu-Heija & Chalabi 1997, Sattar & Greer 2002), but in other studies, in spite of occurrence of pre-eclampsia, hypertension and diabetes, high parity was not considered dangerous (Bubinszki et al. 1999, Roman et al. 2004).

2.2 Hormonal changes during pregnancy

The neuroendocrine system, which controls the human menstrual cycle, induces its effect through the pulsatile gonadotropin secretion, which in turn is regulated by the episodic release of GnRH from the neuronal terminal at the arcuate nucleus. The menstrual cycle is the repetitive expression of the interaction of the hypothalamic-pituitary-ovarian system with associated structural and functional changes in the target tissues – uterus, oviducts, endometrium and vagina. FSH and LH serve as links between the hypothalamus and the ovary. The circulating levels of gonadotropins, oestrogen, progesterone and inhibins during the normal ovulatory cycle in women exhibit well-defined cyclic patterns, consisting of four functional phases, a follicular, an ovulatory, a luteal and a menstrual phase. (Yen et al. 1999b.)

From the beginning of first trimester of pregnancy, the woman is under a storm of hormones from fetal, placental and maternal compartments until delivery. The ovaries
remain inactive throughout pregnancy and the postpartum breastfeeding months. (Speroff et al. 1994.) Maternal immunoassayable LH and FSH levels are virtually undetectable during pregnancy (Yen et al. 1999c). Postpartum amenorrhoea during breastfeeding is induced by the anterior pituitary hormones, oxytocin and prolactin, which regulate lactation and suppress pituitary-ovarian axis functions. Return of cyclic menstruation takes place soon after stopping lactation. (Speroff et al. 1994.)

For steroidogenesis, fetal, placental and maternal compartments form a complete unit, which utilize the maternal compartment as a source for basic building material and as a resource for the clearance of steroids. The placenta synthesises and excretes many releasing and inhibiting hormones, e.g. GnRH which regulates placental steroidogenesis and the release of prostaglandins together with hCG. The placenta produces about 250 mg of progesterone per day, and at term, progesterone blood levels range from 100 to 200 ng/mL, 10 to 20 times more than during the luteal phase of the cycle. Oestrone and oestradiol excretion is increased by about 100 times over nonpregnant levels and oestriol excretion about 1000-fold. Oestrone secretion varies from 2 to 30ng/mL at term, and that of oestradiol between 6 and 40 ng/mL at the 36th week of gestation, increasing thereafter at an accelerated rate. The plateau for oestriol concentration is reached at 31-35 weeks, followed by an increase at 35-36 weeks of gestation. (Speroff et al. 1994.)

HCG is secreted by placental syncytiotrophoblasts. The circulating hCG concentration is approximately 100 IU/L at the time of the expected but missed menses. A maximal concentration of about 100,000 IU/L in the maternal circulation is reached at 8-10 weeks of gestation. The hCG level decreases to about 10,000-20,000 IU/L by 18-20 weeks, and it remains at this level until term. The decline in hCG concentration after the 10th week of gestation occurs at the time of increasing placental progesterone production. (Speroff et al. 1994.)

HPL is also secreted by the syncytiotrophoblasts, and it stimulates IGF-I production. Hypoglycaemia increases and hyperglycaemia decreases the HPL level. These effects may indicate that HPL may work as a fetal growth hormone. During pregnancy, prolactin is secreted by the fetal and maternal pituitary and uterus. During the menstrual cycle, prolactin is mainly of anterior pituitary origin. The decidualised endometrium from the 23rd cycle day onwards is also capable of producing prolactin. Maternal pituitary prolactin stimulates breast growth and prepares it for lactation. Oestrogen and progesterone have an influence on the maturation of the mammary glands for lactation. (Speroff et al. 1994.) All hormonal effects of pregnancy on breasts, the endometrium and ovaries can affect various stages of the multistep processes of carcinogenesis in these organs (Barrett et al. 2003).

The tissues and cells of reproductive organs undergo remodelling and differentiation during pregnancy. Pregnancy also alters blood levels of many regulatory compounds, e.g. the insulin-like growth factors IGF1 and IGF2, and several autocrine growth factors and immune inflammatory cells, which have effects on tissues of the reproductive organs during pregnancy and the postpartum period. (Barrett et al. 2003.) Such substances may induce like hCG early genomic changes that control the progression of the differentiation pathway. These changes are permanently imprinted in the genome, regulating the long-lasting refractoriness to carcinogenesis. (Russo & Russo 2000.)
2.3 Hormonal aspects in cancer risk of GM women

2.3.1 Hormonal risk factors of breast cancer

The development of the breast occurs in three major phases: in uterus, at puberty and during pregnancy, as documented in the rodent. In the fetal period, the growth of epithelial elements into the underlying mesenchyme results in the development of a rudimentary ductal system of the breast. After birth, the mammary ducts remain quiescent. During sexual maturation, the distant ends of the ducts proliferate and develop into the end buds, a structure similar to the human acinus. With the onset of pregnancy, a second round of proliferation occurs. Numerous hormones including oestradiol, progesterone, androgens, prolactin, other lactogenic factors, thyroxin, glucocorticoid, insulin, growth hormones, transforming growth factor $\beta$ and epidermal growth are significant modifiers in this process. (Yen et al. 1999a.)

Breast epithelial ERs are down regulated during the luteal phase of menstrual cycle by progesterone, while PRs remain at a high level until the end of the menstrual cycle. Proliferation of normal breast epithelial cells increases from the follicular to the luteal phase. During the luteal phase, when ERs are down regulated, approximately 1-10% of breast epithelial cells proliferate. In this organ, oestrogen and progestogens may directly and indirectly stimulate proliferation. (Söderqvist 1998.)

Early menarche and late menopause may increase the risk of breast cancer, indicating that long-term cyclic exposure to ovarian hormones is a significant risk factor for this cancer (Kelsey 1993a, Madigan et al. 1998). Recent use of oral contraceptive pills is associated with a modestly increased risk of breast cancer among very young women (Beral & Reeves 1993, Collaborative Group on Hormonal Factors in Breast Cancer 1996, Althuis et al. 2003). HRT, especially the combination of oestrogen and progestins, obviously increases the breast cancer risk, which disappears in five years after finishing this treatment (Collaborative Group on Hormonal Factors in Breast Cancer 1997). In a recent study, the breast cancer risk in current users of preparations containing a combination of oestrogen and progestin increased more (adjusted RR 2.0, 95% CI 1.88-2.12) than for users of preparations containing only oestrogen (adjusted RR 1.30, 95% CI 1.21-1.40) (Beral 2003). Postmenopausal obesity associated with increased oestrogen production also increases the risk of breast cancer (Kelsey et al. 1993a).

2.3.1.1 Reproductive risk factors of breast cancer

Full-term pregnancy has been associated with opposing influences on breast cancer risk; a short term increased risk after childbirth is followed by a long term protective effect against this cancer (Hsieh et al. 1994, Lambe et al. 1994, Rosner et al. 1994). Feto-placental hormones are hypothesised to influence the maternal risk of breast cancer by virtue of their growth-promoting effects on breast cells. During pregnancy, oestrogen and progesterone induce proliferative and differentiative effects on the ductal and lobular-alveolar epithelium. These changes are believed to reduce the susceptibility of breast
tissue to malignant transformation in the long term. (Russo et al. 1982.) The growth-promoting effects of these hormones could also trigger the proliferation of existing tumour cells, leading to an increased risk of breast cancer shortly after pregnancy (Miller 1993). In women with two pregnancies, the short-term adverse effect of the second pregnancy is masked by the long-term protection imparted by the first pregnancy. A plausible biologic interpretation is that pregnancy increases the short-term risk of breast cancer by stimulating the growth of cells that have undergone the early stages of malignant transformation, but that it confers long-term protection by inducing differentiation of normal mammary stem cells, which have potential for neoplastic change. (Bruzzi et al. 1988, Hsieh et al. 1994, Lambe et al. 1994.) Most likely, the protective factor offered by pregnancy at a young age at first birth is hCG, which exerts an inhibitory effect on breast tissue. It starts also the protective differentiation of the breasts, which advances with each subsequent pregnancy (Russo et al. 2000).

During pregnancy, a high concentration of progesterone induces lobular-alveolar development and differentiation for the stage of lactation (Lange et al. 1999), whereas oestrogens stimulate ductal growth (Mauvais-Jarvis et al. 1986). Measuring third-trimester hormone levels in the blood of pregnant women, who were subsequently followed by breast cancer occurrence, showed that elevated progesterone levels were associated with decreased incidence of breast cancer, and this association was stronger for cancers diagnosed at or before the age of 50 years. Increased oestrone levels were associated with an increased incidence of breast cancer overall, whereas such a positive association did not exist for oestradiol. The findings cited above indicate that normal variations in steroid hormone levels during pregnancy could influence subsequent breast cancer development. The mechanism by which pregnancy affects maternal breast cancer incidence is not fully understood. (Peck et al. 2002.) Pre-eclampsia and low birth weight, both associated to the lowered exposure to oestrogen, may predict a lower breast cancer risk (Bernstein 2002). In a recent study placental weight was positively associated with maternal risk of breast cancer in premenopausal women, but among women aged 30 years or younger at first birth, placental weight had no significant association to the breast cancer risk. This finding stresses the importance of the start of breast differentiation at a younger age. (Cnattingius et al 2005.)

Breast cancer is more frequent in nulliparous than parous women (Adami et al. 1990). Protection conferred by pregnancy is observed in women from different countries and ethnic groups, regardless of the endogenous incidence of this malignancy. These observations indicate that this protection does not result from extrinsic factors specific to a particular environmental, genetic or socioeconomic setting, but rather from an intrinsic effect of childbearing on the biology of the breast. (Russo & Russo 2000.) Many studies have explored the association of GM with breast cancer risk. However the number of births of GM women has been small; 93 in a Norwegian study (Kvåle & Heuch 1987, Kvåle et al. 1987), 228 in a Brazilian study (Kalache et al. 1993) and 242 in a Swedish study (Lambe et al. 1996).

Human and animal breast tissues and human breast cell lines contain a low level of hCG receptors and their structural and functional homologue, LH receptors. These gonadotropins have exerted numerous anticancerous effects as seen in breast cancer models and cell studies, which might explain the decreased breast cancer incidence in women with full-term pregnancies. The protective effect of hCG against breast cancer is
based on epidemiological and animal studies, as well as cultural experiments. (Bernstein et al. 1995.) Other studies have also indicated a similar effect of hCG and pregnancy on the expression of certain genes and growth factors which inhibits cell proliferation (Russo & Russo 2000, Russo et al. 2001a).

The RR of mothers with five or more full-term pregnancies has been found to be about 0.5 in comparison with women without any full-term pregnancy (Kvåle et al. 1987, Kelsey et al. 1993a). Despite extensive research, there is still uncertainty concerning the independent effect of parity on breast cancer risk in relation to other reproductive factors. An overview of 26 studies showed conflicting results of the significance of parity and the age at first birth: one found no significant association to the risk with either variable. Seven studies found an association with age at first birth but not with parity; six found an association with parity but not with age at first birth; 12 found an association with both variables (La Vecchia et al. 1989). Increase in parity was associated with an increasing risk of breast cancer in women contracting cancer at under approximately 40 years of age, whereas in older women it appeared to decrease the breast cancer risk. Such a ‘cross-over effect’ has been shown in several studies. (Janerich & Hoff 1982, Adami et al. 1990.)

In meta-analysis of studies from Nordic countries, both parity and age at first birth had an independent influence on breast cancer risk (Ewertz et al. 1990). In a case-control study from Spain analysing the influence of parity, age at first birth and lactation on the risk of breast cancer, parity was found to be an independent risk factor. Women older than 30 years at first birth had an odds ratio of 3.5 (95% CI 1.41-9.83) in comparison with women whose first birth took place before age 21 years. (Ramon et al. 1996.) The cumulative incidence (up to age 70 years) of breast cancer among women who have given first birth before or at age 20 years was 20% lower than that of nulliparous women (Rosner et al. 1994). In a recent review article, older age at first birth increases the risk of breast cancer (Merrill et al. 2005). Kampert et al. (1988) found that delayed menarche and young age at first full-term birth were more protective against breast cancer during premenopausal, than postmenopausal years. Studies about the risk of subsequent births are rare. In the case-control Estonian study, the breast cancer OR for uniparous women, who had the first child before the age of 25 years was 0.62, whereas the ratio for duoparous women, who had both children under this age, was 0.18 (MacMahon et al. 1982). In the study by Kalache et al. (1993), the effect of age at last birth dominated that of age at first birth. This study group also stated that women can considerably reduce the breast cancer risk by completing family planning before the age of 35 years.

Some, but not all, epidemiological evidence suggests, that breastfeeding is protective against breast cancer (Adami et al. 1990, Layde et al. 1989). Whether the age at first breastfeeding is an independent risk factor is unclear (Brinton et al. 1995, Enger et al. 1997). Why lactation is associated with the risk of breast cancer only during premenopausal years, also awaits an answer (Newcomb et al. 1994). A reduced number of ovulatory cycles decreases the risk of breast cancer (Bernstein 2002).

There are two major types of breast cancer, lobular and ductal ones. They are differently dependent on reproductive factors (LiVolsi et al. 1982, Wohlfahrt et al. 1999b). Late age at first birth was associated with an increased risk of lobular but not ductal cancer, whereas lobular cancer had no association with parous status (Wohlfahrt et al. 1999b). The risk for lobular breast cancer among women having given birth to the first
child when older than 30 years was higher than in nulliparous women (LiVolsi et al. 1982). These two types are also different in their hormonal characteristics. Lobular carcinomas have a strong association to ER+. (Wohlfahrt et al. 1999b.) In the study by Ursin and Bernstein, multiparity and early age at first delivery significantly reduced the frequency of ER+PR+ cancer, but had no influence on that of ER-PR- cancers. They also found that parity had a greater protective impact on ductal and ductolobular cancer than lobular cancer, but age at first full-term pregnancy was slightly more protective against lobular cancer. Lactation was associated with reduced risk of both receptor positive and negative cancer. They concluded that the effect of lactation may not be hormonal or at least the mechanisms for this protection are different from those of pregnancies. (Ursin & Bernstein 2005.)

The significance of the effect of reproductive factors on the clinical stage of breast cancer has been evaluated only in a few studies. Wohlfahrt et al. (1999a) suggested, that nulliparity and late age at first birth increased the likelihood of large tumours and nodal metastases.

Familial and sporadic cancer forms may differ from each other in their hormonal aetiology. The increase in the risk of breast cancer associated with a high waist-to-hip measure, low parity, or increase in age at first birth was pronounced among women with a family history of breast cancer. (Sellers et al. 1992.) Reproductive factors other than parity did not correlate to the risk of hereditary breast cancer patients including those with BRCA1 and/or BRCA2 mutations; each pregnancy was associated with an increased cancer risk, and early first pregnancy did not confer any protection (Jernström et al. 1999).

Cellular changes, which occur in the breast and lead to the progression of breast cancer, are thought to be a result of a combination of multiple changes rather than a simple, orderly progression. The loss of the normal regulation of the number of cells, which is one of the first recognisable alterations, results in an abnormal increase in epithelial cells. This is followed by genetic instability and by an abnormal growth and multiplication of cells (atypical ductal hyperplasia). This process may now advance step by step into an in situ, invasive and eventually a metastatic carcinoma. (Russo & Russo 2001c.) In the study by Lagiou et al. (2003) early age at first pregnancy possibly conveyed substantial protection against breast cancer risk among women with benign breast disease, probably operating through the induction of terminal differentiation of mammary gland cells.

### 2.3.2 Hormonal risk factors of endometrial cancer

The endometrial cell division rate increases rapidly in the beginning of the follicular phase, reaching a plateau despite the continuing increase in oestradiol concentration, and then falls quickly to a very low level as a response to the increase in progesterone concentration during luteal phase (Key & Pike 1988). Oestrogen, which is not opposed by progestin, increases the risk of endometrial cancer. "Unopposed-oestrogen hypothesis" supposes that oestrogen induces increased mitotic activity in the endometrial glandular cells (Pike 1990, Key 1995). A high level of endogenous oestrogens is associated with an
increased risk of endometrial cancer (Austin et al. 1991, Nyholm et al. 1993). Until menopause oestrogens are an ovarian product. In postmenopausal women, the primary source of oestrogen is the extraglandular conversion of androstenedione to oestrone and oestradiol. This aromatisation occurs in adipose tissue, which is particularly rich in enzymes facilitating this process. In postmenopausal women the concentration of plasma oestrogen is reduced by 70% to 80% compared to the premenopausal level. (Parslov et al. 2000.) The increased risk associated with obesity in postmenopausal women may be largely due to increased production and bioavailability of endogenous oestrone, although oestradiol might also play a small role (MacMahon 1974, Key & Pike 1988). Diabetes mellitus, mostly due to obesity is a well-known risk factor for endometrial cancer (O’Mara et al. 1985, Maatela J et al. 1994, Stoll 1999).

Combined oral contraceptives are strongly protective against endometrial cancer (Schlesselman 1997). A Danish case-control study showed that oral contraceptives not only protect against endometrial cancer among current users, but protective influence prevails years after cessation of use. In the same study, no relationship was found between early menarche and endometrial cancer risk. (Parslov et al. 2000.) La Vecchia et al. (1984b) demonstrated, on the other hand, that early menarche and nulliparity were associated with an increased risk of endometrial cancer in premenopausal women. This issue is, however, not clear, because in the study by Henderson et al. (1983) no significant relationship was found for these factors. Amenorrhea has been shown to be a risk factor for premenopausal endometrial cancer (Henderson et al. 1983, La Vecchia et al. 1984b) but in the study by Brinton et al. (1992) oligomenorrhea and amenorrhea were without such an association. Progestin-containing IUCD reduces the lifelong risk of endometrial cancer by 55% in 5 years, by 92% in 10 years and by 94% in 15 years (Pike 1990).

HRT without progestin is associated with an increased risk of endometrial cancer (Key & Pike 1988), but a continuous oestrogen and progestin combination nearly eliminates such a risk (Beral 2003).

2.3.2.1 Reproductive risk factors of endometrial cancer

Parity has a strong inverse relation with endometrial cancer risk (Kvåle et al. 1988c, McPherson et al. 1996). In addition, the risk decreased with the number of spontaneous or induced abortions (Parazzini et al. 1991). Nulliparous women have almost twice the risk of uniparous women. The reduction in risk induced by the first pregnancy was more pronounced than that observed for any subsequent pregnancy (Albrektsen et al. 1995b). In other studies, a clear trend of decreasing risk with increasing number of births have been noticed up to the fifth delivery (Henderson et al. 1983, Kvåle et al. 1988c, Brinton et al. 1992, Lambe et al. 1999). In the study by Lambe et al. (1999), the overall effect of parity was stronger against cancer in premenopausal women (<50 years) than in postmenopausal women (≥ 50 years).

Several studies have found an inverse association between increasing age at the last birth and endometrial cancer risk (Kvåle et al. 1988c, Lesko et al. 1991, Parazzini et al. 1998b, Lambe et al. 1999). On the other hand, age at first pregnancy has been
insignificant in this respect (Kelsey et al. 1982, Brinton et al. 1992, La Vecchia et al. 1993). In a Swedish study on women with two or more births, only an older age at last birth remained a significant reducer of endometrial cancer risk (Lambe et al. 1999). In the recent review of studies on cancer, the risk association with early and late age at first birth, young age (19 years or younger) increased endometrial cancer risk (Merrill et al. 2005). Women with the last birth at 40 years or older have been estimated to be at a 44 – 60% lowered risk of endometrial cancer (Kvåle et al. 1988c, Lesko et al. 1991).

The knowledge of the influences of reproductive factors on rare endometrial sarcomas is scanty. Two Norwegian studies demonstrated that different reproductive variables affected the risk of uterine sarcomas in a similar way as in endometrial cancer (Kvåle et al. 1988c, Albrektsen et al. 1995a). Opposite findings have been presented by Schwartz et al. (1991).

The protective effect of prolonged breastfeeding was limited to young women according to the study by Rosenblatt & Thomas (1995). A decreasing trend in risk was observed to accentuate with the lengthening of breastfeeding. The protective effect weakened with time since the cessation of breastfeeding, but there was no evidence of a protective effect after age 55 years even in women who had breastfed for over 5 years. The overall impact of prolonged lactation on the incidence of endometrial cancer cannot be large. (Rosenblatt & Thomas 1995.)

There is no firm biological understanding of how childbearing lowers endometrial cancer risk. The high level of progesterone slows down mitotic activity and stops oestrogen-induced proliferation of the epithelium, thus preventing endometrial hyperplasia and cancerous changes. Progesterone may also make epithelial cells less susceptible to malignant change by promoting differentiation. (Pitot 1986.)

A non-hormonal effect of pregnancy has also been speculated. E.g. birth at an older age may afford protection by mechanically clearing the uterine lining from the cells that have undergone malignant transformation (Albrektsen et al. 1995b, Lambe et al. 1999).

### 2.3.3 Hormonal risk factors of ovarian cancer

In 1971, Fathalla suggested, that chronic repeated ovulation without a pregnancy-induced rest period contributes to neoplasia of the ovarian epithelium. According to the “incessant ovulation” hypothesis, the risk of epithelial ovarian cancer increases with the number of ovulations, as the traumatised epithelium of ruptured follicles is recurrently exposed to oestrogen-rich follicular fluid. (Fathalla 1971.) Growth factors are believed to influence post-ovulatory repair of ovarium epithelium, and impaired regulation of growth factors may be involved in malignant transformation (Riman et al. 1998). Casagrande et al. (1979) extended this concept to a decreased cancer risk for oral contraceptive users by continuous anovulation. In the “gonadotrophin” hypothesis, high levels of pituitary gonadotropins may increase the cancer risk by stimulating ovarian surface epithelium (Riman et al. 1998). Ovulations within the 20-29 years age period are associated with the greatest risk, with a 20% (95% CI 13-26%) increase in risk with each year of ovulation during this age period (Purdie et al. 2003). A new additional hypothesis proposes a pregnancy-dependent clearance of transformed malignant cells from the ovaries (Adami
et al. 1994). Finding, that pregnancy at older ages reduces ovarian cancer risk, supports the view that ovarian surface epithelial cell apoptosis is induced by pregnancy hormones (Whiteman et al. 2003), possibly by progesterone (Risch 1998).

Age at menarche and menopause has been investigated in many epidemiological studies, but conflicting results prove them weak predictors of risk (Riman et al. 2004). Oral contraceptives are known to protect against epithelial ovarian cancer. The RR for epithelial ovarian cancer in a meta-analysis from the 1970s to the 1990s was 0.64 (95% CI 0.57-0.73) among ever-users compared with never-users (Hankinson et al. 1992). Epidemiological studies on HRT and the risk of epithelial ovarian cancer have yielded contradictory results (Riman et al. 2004, Auranen et al. 2005).

### 2.3.3.1 Reproductive risk factors of ovarian cancer

Pregnancy leads to anovulation and suppresses the secretion of pituitary gonadotropins. In line with both the “incessant ovulation” hypothesis and “gonadotrophin” hypothesis theories, pregnancies – especially full-term pregnancies – reduce the risk of epithelial ovarian cancer. (Cramer & Welch 1983.) Parous women compared to nulliparous have ORs of epithelial ovarian cancer in the range of 0.3 to 0.7 (Riman et al. 1998). Analysis of 12 case-control studies revealed a 40% lower risk after the first full-term pregnancy, and each birth thereafter incurred an additional 14% risk reduction (Whittemore et al. 1992). Protection of increasing parity was also found in a large case-control study nested in a nationwide cohort of Swedish women, with a trend of 0.81 per pregnancy (Adami et al. 1994). In another investigation, subsequent pregnancies after the third one did not decrease the risk further (Albrektsen et al. 1996). On the contrary, a minority of investigators have found only a weak or no association between parity and ovarian cancer risk (Tavani et al. 1993, La Vecchia et al. 1984a).

The influence of age at first birth on epithelial ovarian cancer incidence is unclear (Riman et al. 1998). Some investigators report an increased risk for older (Greggi et al. 2000, Mogren et al. 2001) and others for younger age at first birth (Adami et al. 1994, Whiteman et al. 2003). Some investigators have concluded that there is no correlation between age at first birth and ovarian cancer risk (Whittemore et al. 1992, Hankinson et al. 1995b, Merrill et al. 2005). The effect of breastfeeding on ovarian cancer risk is unresolved (Riman et al. 2004).

It has been noticed that there are differences in the significance of reproductive factors for ovarian cancer risk by histological subtypes (Risch et al. 1996, Titus-Ernstoff et al. 2001). In a Norwegian study, the risk of mucinous cystadenocarcinoma increased with increasing parity, whereas in all other types of ovarian cancer the risk decreased (Kvåle et al. 1988b). The later case-control study by Risch et al. (1996) gave similar findings, and the use of oral contraceptives did not have any association with the risk of mucinous cancers. In the population study from Sweden, the increasing parity and decreasing age at first birth significantly decreased the risk of ovarian cancer in different histopathological groups (epithelial, stromal, germ-cell and borderline tumours), but the mucinous tumours were missing (Adami et al. 1994). In another population-based case-control study (Titus-Ernstoff et al. 2001), increasing parity significantly reduced the risk
of serous and endometrioid/clear cell cancers, while the risk of mucinous cancers remained unchanged. Age ≥25 years at first birth reduced the risk of serous borderline tumours and marginally also that of endometrioid/clear cell cancers. Increased age at the last birth decreased the risk of endometrioid/clear cell cancer. The reproductive and menstrual factors had the weakest influence on the risk of mucinous cancers. (Titus-Ernstoff et al. 2001.)

Women with a family history of breast and/or ovarian cancer have an increased risk of ovarian cancer (Auranen et al. 1996, Eerola et al. 2001, Vachon et al. 2002). A recent study on the significance of family history of breast or ovarian cancer revealed that nulliparous women among first-degree relatives were at a much higher risk of ovarian cancer than parous women (Vachon et al. 2002). In contrast, a study on BRCA1 carriers found that parity was associated with increased risk (Narod et al. 1995).

Nulliparity is an established risk factor for epithelial ovarian cancer or borderline ovarian tumour, and infertility, apart from nulliparity, also appeared to increase the risk of epithelial ovarian cancer. Permanently infertile women are at risk for epithelial ovarian cancer, while women with temporary fertility problems have no relation to the risk. (Riman et al. 2004.)

### 2.3.4 Cervical cancer risk factors

It is well established that infection with oncogenic HPV, especially the types HPV16 and 18, is a cause of cervical cancer and its immediate precursor CIN3 (Lehtinen et al. 1996, Walboomers et al. 1999, Wallin et al. 1999). *C. trachomatis* infections also have an important role in the aetiology of cervical cancer (Koskela et al. 2000, Anttila et al. 2001). However HPV infection alone may not be able to cause cervical cancer. Other exogenous and endogenous factors may exist, which in conjunction with HPV would promote the progression of cervical HPV infection to cervical cancer. Candidate cofactors can be classified into three groups: 1) environmental or exogenous cofactors, including the use of oral contraceptives, tobacco smoking, diet, cervical trauma, and coinfection with HIV and other sexually transmitted agents; 2) viral cofactors, such as infection by specific types, coinfection with other types, HPV variants, viral load and viral integration; and 3) host cofactors, including endogenous hormones, genetic factors such as human leukocyte antigen and other host factors related to the host’s immune response. (Castellsague & Muñoz 2003.)

The strongest evidence for the role of oral contraceptives’ use in HPV carcinogenesis derives from the large pooled analysis; the OR for use of oral contraceptive was 2.82 (95% CI 1.46-5.42) for 5-9 years and 4.3 (95% CI 2.09-8.02) for 10 years or longer, and these risks did not vary by time since first or last use. The OR for CIS for 5-9 years’ use of oral contraceptive was 3.4 (95% CI 2.1- 5.5). (Moreno et al. 2002) Mechanisms by which hormonal influences modulate the risk of progression to HSIL/cervical cancer in HPV-infected women are unknown. Transgenic HPV16-expressing mice have been used in experimental studies, which demonstrated synergistic mechanism between long-term estrogen exposure and HPV16 oncogenes in modulating squamous carcinogenesis. More studies will be needed to find out whether the endogenous hormone levels and/or HRT
would be associated with HPV DNA expression and progression to cancer in postmenopausal women. (Castellsague & Muñoz 2003.)

The incidence of cervical cancer in Finland has been low due to the nationwide Pap smear screening programmes, which have been conducted since 1965 with a 5-year interval among women aging from 30- to 60-year old women. The incidence of cervical cancer has, however, increased from 1991 to 1995 in young women (Anttila et al. 1999), possibly owing to increased HPV16 incidence during 1983-97 in this population (Laukkanen et al. 2003).

2.3.4.1 Reproductive risk factors of cervical cancer

High parity has consistently been regarded as a risk factor for cervical cancer (Brinton et al. 1989, Parazzini et al. 1989, Muñoz et al. 2002). Among HPV-positive women, high parity increased the risk of SCC; the OR for cervical cancer in women with seven or more births was four-fold higher than that of nulliparous women, and the risk increased linearly with an increasing number of births (Muñoz et al. 2002). In Costa Rica, the risk for cervical cancer was more than double in women with six or more live births compared to women with none or one birth (Hildesheim et al. 2001). In a review of studies on the role of parity, oral contraceptive use and tobacco smoking in cervical cancer risk, parity seemed to be the cofactor explaining the highest proportion of cervical cancer among HPV-infected women (Castellsague & Muñoz 2003). A strong linear relation of risk to number of births was found among women reporting 14 or more live births; the risk excess being about four-fold compared to women with one or no births (Brinton et al. 1989). The highest risk was noticed in Italian women younger than 45 years with three or more births. Their RR was eight-fold compared to nulliparous women, and it increased with a rising number of births (Parazzini et al. 1998a).

Age at first birth has also been linked to cervical cancer risk. The risk increased in women who had their first birth before 25 years of age, and it decreased in women, whose first birth occurred at an age of 25 years or older. (La Vecchia et al. 1993.) In a large prospective cohort study from Norway, the estimated OR for women with the first birth at 35 years or older was 0.18 (95% CI 0.10-0.31) compared to women with the first birth at age 19 years or younger (Kvåle et al. 1988a). These results were recently confirmed in a Swedish cohort study (Mogren et al. 2001), earlier in a Norwegian register study (Bjorge & Kravdal 1996) and in a fresh review (Merrill et al. 2005). Association of young age at first birth with increased cervical cancer risk is related to young age at first intercourse, which is likewise linked to multiple sexual partners and high parity (Bosch et al. 1992, Guo et al. 1994, Biswas et al. 1997). In some studies the age at first birth is a risk factor only in premenopausal women (Brinton et al. 1987, La Vecchia et al. 1993). In young women the metaplastic cells are in their immature phase of development, which make them susceptible to such injurious changes, which pregnancy and infection factors may cause in this phase of life (Nair & Pillai 1992, Autier et al. 1996).

In multiple linear logistic-regression analysis from India, young age at marriage and short birth interval emerged as the single best predictors of elevated risk of cervical cancer. The results showed that women who married late and had several children are at
greater risk of cervical cancer than women, who married early and had fewer children. In this study, it was not parity per se, which enhances the risk, but rapidity of multiple pregnancies, that matters. (Mukherjee et al. 1994.) In another study after adjustment for parity, “rapidity” of full-term pregnancies was unrelated to the risk of cervical cancer (Muñoz et al. 2002).

There are also studies which do not show any role for multiparity in the aetiology of cervical cancer or CIN (Rotkin 1973, Cuzick et al. 1996). Age at first intercourse and the lifetime number of sexual partners were the most important factors (Cuzick et al. 1996). In the prospective Norwegian study, the risk of cervical cancer was higher in ever married than in never married women, when adjusted for parity or age at first marriage, and age at menarche or menopause did not show any significant associations with SCC (Kvåle et al. 1988a). In addition, the cervical cancer risk has been associated to race, socioeconomics status and sexual behaviour. Low risk of cervical cancer has been observed in such religious groups as nuns, Amish, Jews and Mormons because of lowered exposure to STIs. (Nair & Pillai 1992, Schiffman & Brinto 1995, Schottenfeld & Fraumeni 1996.) A nationwide study from Denmark also noticed that women having children with multiple partners had a higher incidence of cervical cancer than women having children with one partner (Campi et al. 2004).

Incidence of cervical adenocarcinoma has increased recently in Finland, as the Pap screening mainly reduces the incidence of SCC (Anttila et al. 1999). Age-adjusted adenocarcinoma incidence rates has increased about >3% per year (Bray et al. 2005).

In parous women, occurrence of cervical ectopy and squamous metaplasia increases with the number of full-term pregnancies (Autier et al. 1996). High parity may increase the risk of cervical cancer by maintaining the transformation zone on the ectocervix for many years, thus facilitating this zone to the direct exposure of HPV and other possible cofactors (Muñoz et al. 2002). Hormonal changes induced by pregnancy (increased levels of oestrogen and progesterone) may also modulate the immune response to HPV and have an influence on the risk of persistence or progression of malignancy (Muñoz et al. 2002, Castellsague & Muñoz 2003).

2.4 Hormonal and reproductive risk factors of other cancers of GM women

Hormones may play a significant role in the aetiology of some non-gynaecological cancers. Case-control studies have shown that parity may increase the risk of renal cell cancer not only by hormonal or metabolic changes, but also via obesity and hypertension. (Mellengaard et al. 1994, Chow et al. 1995.) Compared to nulliparous women, everparous women had a 40% increased risk of renal cell cancer (Lambe et al. 2002). ERs and PRs have been identified in normal and malignant renal cells (Ronchi et al. 1984). It has been speculated that pregnancy-associated hormonal changes, particularly high oestrogen level, may act as a promoter of malignant transformation by stimulating renal cell proliferation, either directly or via paracrine growth factors (Concolino et al. 1993). Ovarian hormones may also influence bladder cancer risk. Growth and oncogenesis of transitional cell tissue of bladder is responsive to steroid hormones at least in laboratory
conditions (Reid et al. 1984). Cigarette smoking might still be the most powerful risk factor for bladder cancer (Pelucchi et al. 2002). However, parous women had a decreased bladder cancer risk compared to nulliparous women (OR 0.67, 95% CI 0.44-1.00) after adjustment for age, smoking and previous bladder infection (Cantor et al. 1992).

Gender differences in the histological distribution of lung cancer and a possibly greater susceptibility of women than men to tobacco carcinogens, suggest that sex-specific hormones may play a role in the genesis of lung cancer (Risch et al. 1993, Caracta 2003). Siegfried has hypothesised that oestrogen may have an influence on lung cancer development, either through direct promotion of lung cell proliferation, on lung carcinogen metabolism or on the development of lung diseases, which predispose to this malignancy (Siegfried 2001). The presence of ERs and other steroid receptors in lung tissue has been confirmed (Beattie et al. 1985, Cagle et al. 1990). A reduced lung cancer risk was observed in women with a history of use of oral contraceptives or HRT, but age at menarche, number of births and age at menopause had no association (Kreuzer et al. 2003).

Incidence and mortality of gastric cancer are at all ages about two times higher in males than in females (Levi et al. 1994). This difference has been speculated to be a consequence of hormonal differences. Female sex hormones might counteract the development of gastric cancer. This hypothesis gets support from experimental studies. Oestrogen treatment suppressed the development of gastric cancer in male rats (Furukawa et al. 1982). ERs and PRs are present in gastric mucosa, cancer tissue and cancer cell lines (Wu et al. 1990). In addition, there is evidence, that pregnancy might accelerate the growth of gastric cancer (Furukawa et al. 1994). In a Norwegian cohort study the risk of gastric cancer according to the childbearing history differed significantly between pre- and postmenopausal women and between subsites of gastric cancer (Heuch & Kvåle 2000). In a prospective cohort study from Japan, multiparity conferred a tendentious protection from death of gastric cancer (Kaneko et al. 2003). Possible confounding by dietary habits, lifestyles, socioeconomic status and even infection with Helicobacter pylori should be taken into consideration in studies on the aetiology of gastric cancer (Kaneko et al. 2003).

Hormonal and reproductive factors have been thought to play a role in women with cancer of colon and rectum similarly to that of breast cancer (e.g. increasing parity and early age at first birth are protective). (La Vecchi et al. 1992.) Endogenous and exogenous female hormones may influence the colorectal cancer risk by interfering with the hepatic bile acid metabolism (McMichael & Potter 1980). In the study by Peters et al. (1990) the relationship between the number of pregnancies and colon cancer risk was actually U-shaped; decreasing risk with successive pregnancies up to the fourth birth followed by increasing risk with additional pregnancies, suggesting the presence of competing factors. Another study, however, demonstrated, that the risk of colon cancer, but not rectal cancer, decreased significantly with an increasing number of births. HRT has reduced the risk of rectal cancer, whereas oral contraceptives did not induce this response. (Talamini et al. 1998.)
2.5 Hormonal and reproductive risk factors of other diseases of GM women

The role of endogenous hormones in the aetiology of cardiovascular disease is of considerable interest. The available data pertaining to disease risk in relation to endogenous hormones, menstrual cycle patterns, gravidity, parity and age at first birth are limited. GM women were associated with a small but consistent increase in the risk of coronary heart and cardiovascular diseases. (Ness et al. 1993.) Repeated pregnancies may result in permanent detrimental effects on lipid and glucose metabolism (Sattar & Greer 2002) and maternal obesity is associated with dysregulation of metabolic, vascular and inflammatory pathways (Ramsay et al. 2002). In a Rotterdam study, parity was positively associated with BMI, total cholesterol/HDL ratio, insulin resistance, age at menopause and socioeconomic status (Humphries et al. 2001). In a British study, the number of children was positively associated with body mass index, waist-hip ratio, triglycerides and diabetes and inversely with HDL concentration (Lawlor et al. 2003).

Gravidity and parity appear to be associated with an increased risk of diabetes mellitus, hyperlipidemia, coronary heart (Kritz-Silverstein et al. 1989, Ness et al. 1993, Ness et al. 1994) and also cerebrovascular diseases (Qureshi et al. 1997). The risk for intracerebral haemorrhage was three-fold higher in women who had been pregnant compared with nulligravid women. The risk was reduced after adjustment for potential confounders, suggesting, that differences in socioeconomic status, race, previous heart disease, diastolic blood pressure and diabetes mellitus may play a role in the causal pathway between pregnancy and stroke. (Qureshi et al. 1997.)

The role for oestrogen in neuroprotection is unclear. Oestrogen may act through several routes including oestrogen dependent alterations in cell survival, axonal sprouting, regenerative responses, enhanced synaptic transmission and enhanced neurogenesis. (Garcia-Segura et al. 2001.) The effect of HRT on cognitive function in women is unclear (Hogervorst et al. 2000). Parity resets ovarian function into permanently lower oestrogen production in parous women compared with nulliparous women (Hankinson et al. 1995a). Effects of oestrogen on cognitive disorders are poorly understood. Ptok et al. (2002) speculated that natural oestrogen would reduce the risk of Alzheimer disease. A pregnancy-induced lack of natural oestrogen might be detrimental. The impact of fetoplacental hormones on cognitive functions has never been investigated thoroughly as far as it is known. The impact of children on the parental suicide rate has also been insufficiently examined. Married, parous women had a lower RR for suicide than married nonparous women at all ages. (Hoyer & Lund 1993.) In this study, there was a strong linear decrease in RR for suicide during premenopausal and postmenopausal years with an increasing number of children. The effect of the number of children was independent of social class measured by years of completed schooling. These findings provide empirical support for theories of associations of parenthood with suicide first presented by Durkheim (1897). Similar results have been obtained in some other studies (Isometsä et al. 1996, Qin & Mortensen 2003). The children may increase the parents’ feelings of self-worth, possibly based on their perception of being needed, or children would provide emotional and material support to parents when they have difficulties or setbacks. The effect of possible selection bias cannot be excluded; people in good
physical and mental health or generally living a happy life are the most likely to have children. (Qin & Mortensen 2003.)

2.6 General aspects of the effect of childbearing on mortality of GM women

Fertility can affect health in several ways. They include direct biological effects, selection effects, and indirect effects such as the relative costs and benefits of birth of children. The direct effects of fertility include the physiological consequences of pregnancy and childbirth. It is not surprising that results from empirical studies are in some respects confusing or conflicting. Furthermore, some of the associations described might be confounded by socioeconomic and socio-demographic characteristics. (Grundy & Tomassini 2005.) Additionally, there are well-established linkages between some aspects of fertility patterns and certain diseases, most notably breast cancer (associated with nulliparity and delayed motherhood) (Madigan et al. 1995).

There are few data which systematically relate women’s, especially GM and GGM women’s, reproductive histories to their long-term health. A record linkage study on the mortality and health status after 50 years follow-up of women born 1911-1940 in England and Wales showed that nulliparous women and women with five or more children had a significantly higher mortality than other women. Mortality was also raised in the group of oldest women with just one child and mothers with short birth intervals, including mothers of twins. Childbearing after the age of 39 years was associated with lowered mortality. (Grundy & Tomassini 2005.) The impact of family status and employment status explored in Finland and Sweden showed that married women who were employed and lived in couples with children, had the best health in both countries (Roos et al. 2005).

“A tooth per child” is an old phrase. It is known that caries and loss of teeth increase the risk of diseases and death (Paine 1997). A Danish study on twins born between 1893-1923 and interviewed in 1995-1997, showed that women with low social status lost about one tooth per child, whereas women of high social status lost about one tooth per two children (Christensen et al. 1998).

2.6.1 Mortality in gynaecological and other cancers

In England and Wales between 1938 and 1960, ever-married parous women had lower mortality from breast, ovarian and endometrial cancer than nulliparous women, but a higher mortality in cancer of the uterine cervix. The all-causes SMR in the year 1959-60 was 20% higher in parous than in nulliparous married women. (Beral 1985.) The same research centre reported later, that women who had never had children, had a higher SMR (113) than parous (97) women (p<0.01). The mortality of parous women increased significantly for cervical cancer and decreased for breast, oesophageal, kidney and bladder cancer compared to nulliparas. An increasing number of births was insignificant
for ovarian and endometrial cancer mortality. In this study, the women were married and adjusted also for their husband’s social class. (Green et al. 1988.)

In a prospective Norwegian study, there was a highly significant inverse association between parity and all-cause mortality in young women and a moderate direct association among women aged ≥50 years. Parity was inversely associated with the incidence of breast, endometrium, ovarian, melanoma and other skin cancers. Positive associations were observed for the incidence of cervix cancer, cancers of the respiratory system of old women, pancreatic cancer and multiple myelomas of young women. (Kvåle et al. 1994.)

2.6.2 Mortality in other diseases and accidents

The parous women had higher mortality from diabetes mellitus, gallbladder diseases, nephritis and nephrosis, hypertension, ischemic and degenerative heart diseases, cerebrovascular diseases and all cause of death by Beral (Beral 1985). Mortality from circulatory diseases, including hypertensive disease, ischemic heart disease, and subarachnoid haemorrhage, tended to rise with increasing parity in another British study from the same centre (Green et al. 1988).

In a large Norwegian study, mortality for several diseases and accidents in parity categories up to five has been studied. Significant increasing mortality from diabetes mellitus, cerebrovascular and ischemic heart diseases with increasing parity was observed in the older part of the cohort. Deaths from diseases of the respiratory system and suicide were most common among nulliparous women. Parity was associated with an increased risk for accidents, poisoning and violence even though the differences were not statistically significant. (Kvåle et al. 1994.)
Purpose of the present study

Pregnancies may cause many changes in endocrinologic and metabolic functions of women and also complications which may have an influence on the lifelong health of women. These questions have never before been extensively investigated among large populations of GM and GGM women, although such information would be of utmost significance for women planning to have several children. Excellent and extensive Finnish population based registers offered an ideal opportunity to search for answers to these questions.

The specific aims of the study:

1. To determine the incidence of breast, endometrial, ovarian and cervical cancer among GM women as compared to the general female population.
2. To determine the independent effects of parity, age at first birth, birth interval (= density of births) and birth period (time from first to last birth) to the risk of breast, endometrial, ovarian and cervical cancer in the population of GM women using multivariate regression models.
3. To investigate the overall and cause specific mortality – not only cancer mortality – among GM women using SMR estimates.
4 Subjects and methods

4.1 Population-based cohort from registers

The personal identifiers of all 86,978 GM women with at least 5 deliveries and dates of birth of all their children up to 31 December 1997 were extracted from the files of the Finnish Population Register, which includes links between parents and children since 1974. Follow-up for cancers of breast, cervix uteri, corpus uteri and ovary was done electronically through the files of the national, population-based Finnish Cancer Registry using personal unique identifiers as the key. Every Finn has had this unique personal identification code since 1967, and it has been used in all national main registers. The number of GGM women in the GM cohort was 3752.

Most of the GM women in Finland belong to the Laestadian religious movement within the Lutheran Church. High parity is common within this movement, as any kind of contraception is forbidden (Sipilä et al. 1988), but other life habits are not known to differ markedly from those of average Finns. However, they do not normally use alcohol. Smoking among pregnant Finnish women is very rare, and during the years 1987-2002 GM women smoked about three-times less often than other pregnant women in Finland (Stakes 2002).

The Finnish GM women are living all around Finland. During the study period, GM women represented 2.6% of all parturient in the north, and 0.5% in the southern Finland. In the 1990s about 50 percent of the GM women were economically active, and about 80% of them were entrepreneurs (mainly independent farmers) or white collar workers. The respective proportions in the general female population were 75 percent and 65%. The GM women are nearly always married; during the mid 1990s about 95% of the GM women were married, while the percent among all the other parturient was 67%. (Stakes 2002.)
SIRs were calculated to compare the incidence of breast, endometrial, ovarian and cervical cancers among GM women with that in the entire Finnish female population. The follow-up started from the birth of the fifth child or on the first of January 1974, whichever was later, and ended at emigration, death or on the 31st of December 1997, whichever was earliest. After the analyses published in separate articles of this thesis, the cancer data was updated up to the year 2002. The number of person years up to year the 2002 was 2.0 million.

The numbers of observed cases of cancers and person-years at risk were counted by five-year age groups and by calendar periods. The expected numbers of cases were calculated by multiplying the number of person-years in each stratum by the corresponding incidence rate in Finland. The SIR was calculated by dividing the number of observed cases by the number of expected cases. The 95% confidence intervals (95% CI) for the SIRs were based on the assumption that the number of observed cases presents a Poisson distribution. The cohort was stratified according to parity (5, 6, 7, 8+ children), age at first birth (< 20, 20-24, 25-29 and 30+ years), birth interval (< 2.0, 2.0-3.0, 3.0+ years) and age at follow-up (<40, 40-49, 50-64 and 65+ years).

The conditional logistic regression was used in the case-control design nested in the GM cohort to estimate proportional hazards by different factors. For each woman with cancer by the end of year 1997, 50 reference women were randomly selected from the cohort except in ovarian cancer in the year 2003. The controls had to have the same year and month of birth as the case woman, to be alive in Finland and free of cancer at the date of diagnosis of the case. These analyses were performed using the SAS statistical software (SAS, 1997).

In addition to the data described above, we categorised the age in two broad categories: “premenopausal” (< 50 years) and “postmenopausal” (50+ years) women. In postmenopausal women, most of whom had already had their last child, the significance of the length of the entire birth period, i.e. years from the first to last birth, were analysed (<10, 10-14.9, 15-19.9 and 20+ years) and the period between the last birth and age 50 years (<10, 10-14.9 and 15+ years) was studied for endometrial cancer (Study II). In ovarian cancer (Study V), the significance of the birth period (the average interval between the first and last deliveries, categorised to <10 years, 10-14.9, 15-19.9, and 20+ years), and the time between the last birth and cancer (<10, 10-19.9, 20-29.9 and 30+ years) were also analysed for woman 50 years or older.

The Cancer Registry data includes information on the histopathological diagnosis and clinical stage (local, regional and distant diseases) made by local pathologists. In ovarian cancer we did not investigate the clinical stage at all, and in endometrial cancer only two categories were used (local and nonlocal diseases). All cases of ovarian cancer were reclassified by using free-text data (included in the Cancer Registry data base) on cancer topography and morphology, because the historical standard Cancer Registry classification of histological types did not separate the cases into modern categories as needed for our analyses.
4.3 Overall and cause specific SMR of GM women

A study cohort of all GM women in Finland (N = 87,922, the whole GM cohort) and of those 3678 GGM women from 1 January 1974 to 31 December 1997, were drawn from the national population register. A record linkage was made with the national cause-of-death file of Statistics in Finland using the unique personal identification code up to the year 2001. Deaths had been classified according to the International Classification of Diseases (the 8th version in 1969-1986, the 9th version in 1987-1995 and the 10th version in 1996-2001). Person-years were calculated from the 5th/10th birth or 1 January 1974, whichever was later, until death or 31 December 2001 by 5-year age groups. SMRs were defined as the observed to expected number of deaths by using cause-specific mortality among all Finnish women as a reference. The confidence intervals for the SMR were based on the Poisson distribution.

The study design and study population is presented in Fig. 1.
Fig. 1. The study design and study population from Finnish registers of 1974-1997 (year 1974-2002).
5 Results and Comments

5.1 SIRs and SMRs of gynaecological cancers

The overall cancer incidence of GM women (1974-2002) was low (SIR 0.80, 95% CI 0.78-0.81; N= 10,137). There were 2045 breast, 545 endometrial, 418 ovarian and 271 cervical cancer cases in the GM cohort. SIRs were low in breast, endometrial and ovarian cancer among GM women, and they were of a relatively similar magnitude. Eighty-eight% of the reduction in the overall SIR among GM women was based on the markedly diminished death rate in hormone dependent gynaecological cancers. The SIR of cervical cancer was increased. The SIRs for breast, endometrial and ovarian cancer among GGM women were lowered about 50%, but in cervical cancer the incidence was close to that of national population (calculated in birth category 8+). (Table 2)

Table 2. The SIRs with 95% CI of gynaecological cancers in whole cohort (1974-2002) and separately in cohorts of GM women, birth category five to nine and GGM women (1974-1997).

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>Obs</td>
<td>Exp</td>
<td>SIR</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2045</td>
<td>3621</td>
<td>0.56</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>545</td>
<td>960</td>
<td>0.57</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>418</td>
<td>657</td>
<td>0.64</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>271</td>
<td>231</td>
<td>1.17</td>
</tr>
</tbody>
</table>

*Birth category five to seven.
** Birth category from eight onwards
The SIRs of breast and endometrial cancer were slightly lower in pre- than postmenopausal women, whereas in ovarian cancer the lowest SIR was seen during the early postmenopausal period. In cervical cancer, the SIR was significantly higher than the national average only in premenopausal GM women. (Table 3)

Table 3. The SIR with 95% CI of gynaecological cancers of GM women according to age at diagnosis.

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Age at diagnosis &lt; 50 years</th>
<th>Age at diagnosis 50-64 years</th>
<th>Age at diagnosis 65+ years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs</td>
<td>Exp</td>
<td>SIR</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>222</td>
<td>467</td>
<td>0.48</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>27</td>
<td>53</td>
<td>0.51</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>50</td>
<td>78</td>
<td>0.63</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>57</td>
<td>36</td>
<td>1.58</td>
</tr>
</tbody>
</table>

The proportion of ductal breast cancer was 67% and that of lobular cancer 8%, while the rest (25%) represented anaplastic cancers and some rare histological subtypes of the total of 1,508 breast cancers diagnosed during 1974-1997. The SIR was low in each subtype; in ductal cancer 0.53 (95% CI 0.50-0.56; n=1017), in lobular cancer 0.51 (95% CI 0.42-0.60; n=123) and 0.59 (95% CI 0.53-0.66; n=368) in the remaining cancers. The incidences differed between clinical stages; the SIR was highest in distant 0.66 (95% CI 0.53-0.78; n=101) and lowest in local 0.50 (95% CI 0.46-0.53; n=738) breast cancer.

Eighty-eight per cent of endometrial carcinomas were adenocarcinomas. The malignancy was local in 84% of the cancers. The incidence of sarcomas was nearly the same as the national average (SIR 1.02, 95% CI 0.63-1.56). The SIRs were nearly identical in local (SIR 0.58, 95% CI 0.51-0.65; n=303) and more advanced (0.58, 95% CI 0.44-0.76; n=58) endometrial cancer.

The incidences were significantly decreased in each histological subtype of ovarian cancer, except in granulous-stromal cell tumours (SIR 1.03, 96% CI 0.52-1.85; n=11). The SIR for serous cancer was 0.69 (95% CI 0.59-0.78; n=184), endometrioid cancer 0.43 (95% CI 0.34-0.53; n=80), mucinous cancer 0.82 (95% CI 0.62-1.05; n=59) and borderline tumour 0.74 (95% CI 0.58-0.92; n=76).

Eighty-six per cent of cervical cancers were SCCs and 14% adenocarcinomas. The SIR was below the national average in adenocarcinoma (SIR 0.77, 95% CI 0.52-1.10; n=30) but above in SCC cases (SIR 1.21, 95% CI 1.05-1.40; n=190). There was some variation between the clinical stages of cervical cancer. In the regional cancer the SIR was significantly high (SIR 1.74, 95% CI 1.09-2.64; n=22), whereas in the local (SIR 1.17, 95% CI 0.97-1.41; n=111) and advanced (SIR 1.08, 95% CI 0.83-1.39; n=62) forms, no significant increase in the SIR was observed.

In breast, endometrial and ovarian cancer, the SMR was higher than the respective SIR. The SMR was highest in cervical cancer, and it did not differ from the respective
SIR. The SIR and SMR for all gynaecological cancers were 0.59 (95% CI 0.57-0.61), and 0.68 (95% CI 0.64-0.72) for GM women. The SMR, 0.60 (95% CI 0.42-0.84) for GGM women was smaller than for GM women. The SMR of breast cancer in GM women was a little bit smaller than in GGM women, whereas in endometrial, ovarian and cervical cancers it was smaller in GGM than GM women. (Table 4)

Table 4. The SMRs with 95% CI of gynaecological cancers among GM and GGM women 1974-2001.

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>GM women</th>
<th>GGM women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs Exp</td>
<td>SMR 95%CI</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>633  987</td>
<td>0.64 0.59-0.69</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>123  182</td>
<td>0.68 0.56-0.80</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>279  412</td>
<td>0.68 0.60-0.75</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>120  109</td>
<td>1.10 0.92-1.31</td>
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5.1.1 Comments

A homogenous and large national cohort of nearly 90,000 GM women offers good ground for this study. The number of cancer cases in different cancer types and subcategories is big enough for reliable SIR and RR calculations, nearly always in GM cohort but less commonly in GGM women’s group.

The number of breast cancer cases (n=1508) among GM women was much bigger than in the earlier studies; n=93 (Kvåle et al. 1987a, Kvåle & Heuch, 1987b), n=228 (Kalache et al. 1993) and n=242 (Lambe et al. 1996). Most of the previous respective epidemiological studies have been conducted using a case-control setting without GM women. Norwegian studies on different cancer types, however, were population-based, but the number of GM women was relatively small (Kvåle et al. 1987a, Kvåle & Heuch, 1987b, Kvåle et al. 1988a, Kvåle et al. 1988b, Kvåle et al. 1988c, Kvåle et al. 1994). There are only a few studies on cervical cancer exploring these questions with a sufficient number of GM women (Brinton et al. 1989, Hildesheim et al. 2001, Muñoz et al. 2002).

The overall cancer incidence in this study was 8% lower than that in the prospective cohort study from four Norwegian counties (SIR 0.88, 95% CI 0.80-0.96). Present SIRs in each gynaecological cancer are presented together with the respective recordings extrapolated here by specific calculations from the Norwegian results (Table 5). (Kvåle et al. 1994.)
Table 5. The SIR with 95% CI of gynaecological cancers in whole GM women in Finland 1974-2002 and 1974-1997 and in Norway (GM women compared to women with two children) (Kvåle et al. 1994).

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<tr>
<td>Cervical cancer</td>
<td>271</td>
<td>231</td>
<td>1.17</td>
</tr>
</tbody>
</table>

¹Modified SIRs of Norwegian study; age groups < 50 and ≥ 50 years were computed and SIRs with 95% CI were first calculated for both parity groups, thereafter GM women were compared to 2+ women.

The SIRs of breast and ovarian cancer were similar for GM women in both countries (Table 5). The risk reduction varied between about 43-45% for breast and 34-35% for ovarian cancer in these studies. The risk of GM women to contract cervical cancer was much bigger in Norway than in Finland, but the risk of endometrial cancer tended to be bigger in Finland than in Norway. (Kvåle et al. 1994.) The low risk of cervical cancer in Finland compared to other countries, in spite of a modestly increased SIR in our population, emphasises the importance of organised Pap smear screening in Finland in the fight against this malignancy (Anttila et al. 1999).

Including all age groups at diagnosis, the decrease in the SIR of breast, endometrial and ovarian cancers of GM women varied between 23-52% (Table 3). The decrease in breast and endometrial cancer risk and the rise in cervical cancer risk were most prominent during premenopausal years. As regards cervical cancer, similar results have also been previously presented elsewhere (Muñoz et al. 2002), but in the Norwegian study both pre- and postmenopausal women had an increased risk of getting cervical cancer (Kvåle et al. 1994).

The SIR was similarly decreased in ductal and lobular breast cancer. In endometrial adenocarcinoma, the SIR was low in the whole population, but in sarcomas unchanged as compared to the national average. Norwegian studies (Kvåle et al. 1988c, Albrektsen et al. 1995b), demonstrated a decreasing risk with an increasing number of births also in sarcomas.

The incidence of granulos-stromal cell tumour in ovarian cancer was about the same as the national average, and in other types decreased. In another study the incidence was decreased in all ovarian cancer types (Adami et al. 1994). In comparison to our results, the incidences of mucinous and nonmucinous tumours were different, but those of invasive and borderline tumours were similar (Risch et al. 1996).

Our study evaluated the effect of multiple births on the mortality of gynaecological cancers for the first time. According to our study, GM and GGM women had decreased SIRs and SMRs for cancer of breast, endometrium and ovary and increased for cervical cancer. The number of GGM women for SMR calculation was relatively small in cancer.
diseases. Protective influence of pregnancies against breast, endometrial and ovarian cancer has been found previously in women with less than 5 births compared to nulliparas (Beral 1985, Green et al. 1988, Kvåle et al. 1994). The SMRs for breast, endometrial and ovarian cancer were somewhat higher than the respective SIRs among the present GM women, at least partly owing to varying practices in registration of the cause of death in different centres.

5.2 RRs of gynaecological cancers according to reproductive parameters

In multivariate analysis the RR of breast and endometrial cancers decreased with increasing parity (Table 6). Women with at least eight deliveries had a nearly 30% lower risk of breast and endometrial cancer than the 5-para. In ovarian and cervical cancer the risk did not decrease or increase with a rising number of deliveries from 5 to 8+.

Young age at first birth was protective for breast cancer, while for endometrial and cervical cancer old age had a similar effect. This variable remained insignificant for ovarian cancer. In breast cancer 63% of GM women were younger than 25 years at first birth. Respective figures were 68% in endometrial cancer, 65% in ovarian cancer and 68% in cervical cancer. A short birth interval between births was protective in breast cancer while in endometrial and cervical cancer it tended to weaken the protection.

Multivariate analysis was also performed separately for premenopausal and postmenopausal GM women (50 years or less and > 50). Because only 12% of ovarian cancer was premenopausal, the whole cohort was handled as postmenopausal. The protective effect of parity in breast cancer was stronger in postmenopausal than premenopausal GM women, while late age at first birth increased the breast cancer RR 3.1-fold in premenopausal but only 1.4-fold in postmenopausal women. In endometrial cancer the RR increased in premenopausal women with increasing parity, but in postmenopausal women it significantly decreased. The decreased endometrial cancer risk by old age at first birth was seen in both age categories. In cervical cancer this phenomenon appeared in premenopausal women.

In postmenopausal women the RR of endometrial cancer in relation to the birth period was more than 40% smaller in women with a birth period longer than 20 years than in women with a birth period shorter than 10 years. A short premenopausal delivery free period was also protective in this disease.

In postmenopausal GM women the RR was calculated for histological subtypes of breast and ovarian cancer. Increasing parity decreased the ductal breast cancer risk, while in lobular cancer a short birth interval influenced similarly. Old age at first birth was a significant risk factor in both cancer types. In ovarian cancer none of the reproductive variables had a significant effect on the RR in any histological subtype.

Increasing parity decreased the RR of local breast cancer whereas increasing age at first birth increased the RR of distant breast cancer to 1.4-fold as compared to those with first birth at age less than 20 years. The risk of distant breast cancer was highest among premenopausal GM women.
Table 6. RRs of study variables with 95% CIs of breast, endometrial, ovarian, cervical cancer cases among GM women in multivariate analysis. Observed numbers (Obs) are also given. Data from 1974-1997, only for ovarian cancer from 1974-2003.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Breast cancer</th>
<th>Endometrial cancer</th>
<th>Ovarian cancer</th>
<th>Cervical cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs</td>
<td>RR 95%CI</td>
<td>Obs</td>
<td>RR 95%CI</td>
</tr>
<tr>
<td>Birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>855</td>
<td>1.00 Ref</td>
<td>231</td>
<td>1.00 Ref</td>
</tr>
<tr>
<td>6</td>
<td>396</td>
<td>0.88 0.78-1.00</td>
<td>101</td>
<td>0.72 0.57-0.92</td>
</tr>
<tr>
<td>7</td>
<td>120</td>
<td>0.81 0.67-0.99</td>
<td>42</td>
<td>0.87 0.62-1.22</td>
</tr>
<tr>
<td>8+</td>
<td>137</td>
<td>0.76 0.62-0.92</td>
<td>45</td>
<td>0.71 0.57-1.02</td>
</tr>
<tr>
<td>Age at first birth (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>176</td>
<td>1.00 Ref</td>
<td>56</td>
<td>1.00 Ref</td>
</tr>
<tr>
<td>20-24</td>
<td>774</td>
<td>1.33 1.12-1.57</td>
<td>231</td>
<td>0.94 0.64-1.26</td>
</tr>
<tr>
<td>25-29</td>
<td>421</td>
<td>1.52 1.26-1.84</td>
<td>108</td>
<td>0.77 0.55-1.10</td>
</tr>
<tr>
<td>30+</td>
<td>137</td>
<td>1.83 1.43-2.34</td>
<td>24</td>
<td>0.58 0.34-0.97</td>
</tr>
<tr>
<td>Birth interval (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.0</td>
<td>399</td>
<td>1.00 Ref</td>
<td>120</td>
<td>1.00 Ref</td>
</tr>
<tr>
<td>2.0-3.0</td>
<td>592</td>
<td>1.06 0.93-1.21</td>
<td>170</td>
<td>0.94 0.73-1.19</td>
</tr>
<tr>
<td>3.0+</td>
<td>517</td>
<td>1.15 1.00-1.34</td>
<td>129</td>
<td>0.83 0.63-1.10</td>
</tr>
</tbody>
</table>
Present results of the protective effect of an increasing number of pregnancies on breast and endometrial cancer agree with earlier findings (Kelsey et al. 1993b, Ramon et al. 1996, Kvåle et al. 1987a, Lambe et al. 1996, Kvåle et al. 1988c, McPherson et al. 1996). The protective effect extends to the eighth birth in breast cancer and to the sixth-eight birth in endometrial cancer, i.e. higher than previously reported (Henderson et al. 1983, La Vecchia et al. 1989, Kvåle et al. 1988c, Brinton, 1992, Lambe et al. 1999). The results in ovarian cancer are in line with the Norwegian results, showing no further reduction in risk after the third-fifth delivery (Albrektsen et al. 1996). This observation specified our knowledge of the decreasing effect of parity on ovarian cancer risk as very precise (Whittemore et al. 1992, Adami et al. 1994).

The incidence of cervical cancer among GM women was slightly bigger than the average. The RR estimates in other studies have been higher than the RR of 1.13 in our study – fourfold in women with seven or more full-term pregnancies compared to nulliparas (Muñoz et al. 2002). In a study on women with 14 or more births, the excess risk was four-fold compared to women with one or no births (Brinton et al. 1989). The highest RR of 8.1 for cervical cancer in women with three or more births compared with nulliparous was recorded in Italy (Parazzini et al. 1998). It should be borne in mind that the RR estimates in this study would have been larger, if the reference women would have been nulliparas.

Young age at first birth in the present population was a significant risk reducer in breast cancer. The review of 26 studies did not result in any consensus about the significance of parity and age at first birth in breast cancer (La Vecchia et al. 1989). There is, however, a more recent review of studies on the importance of reproductive risk factors in gynaecological cancers with conclusions similar to our observations. Hence, young age at first birth diminishes the risk of breast cancer, increases the risk of endometrial and cervical cancer and is without any significance in ovarian cancer risk. (Merrill et al. 2005.)

A short interval between births was protective in breast cancer, but its effect in endometrial and cervical cancer was opposite. The effect of the birth interval in cervical cancer was the best single predictor of elevated risk in the study by Mukherjee et al. (1994). However, another study could not confirm this finding (Muñoz et al. 2002).

Gynaecological cancers differ markedly from each other in their hormonal relationships as seen in the present RR evaluations of the whole population and pre- and postmenopausal groups. The protective effect of parity on breast cancer was stronger in post- than premenopausal GM women. Our results support the ‘cross-over effect’, that has been shown several times (Janerich & Hoff 1982, Adami et al. 1990). In endometrial cancer the protective effect of parity manifested itself only during the postmenopausal years in our study. There are also results of protection before the menopause (Lambe et al. 1999). In cervical cancer the risk increasing effect of young age at first birth was stronger in premenopausal than postmenopausal women in this and earlier studies (Cuzick et al. 1996, Brinton et al. 1987). The transformation zone in the cervix is susceptible to the carcinogenic effects of HPV and C. trachomatis, particularly in young women (Autier et al. 1996, Nair & Pillai 1992).
The birth period was an important risk factor only in endometrial cancer. A period over 20 years decreased its risk in postmenopausal women. A short premenopausal delivery-free period, a new risk factor, proved useful by confirming that the short period reduces endometrial cancer risk. Our results support previous observations of the protective effect of old age at last delivery in this disease (Lambe et al. 1999, Merrill et al. 2005).

The major types of breast cancer, ductal and lobular ones, have different relationships to ovarian hormones and reproductive factors (Wohlfahrt et al. 1999b, LiVolsi et al. 1982 Mauvais-Jarvis et al. 1986). Our results agree with this view; parity was protective in ductal but not in lobular cancer, and a short birth interval in lobular but not in ductal cancer. Older age at first birth increased the risk of both histological subtypes. There are opposite results too; old age at first birth was associated with an increased risk of lobular but not ductal cancer (Wohlfahrt et al. 1999b, LiVolsi et al. 1982). Multiparity and young age at first delivery may affect the hormonal characteristics of breast cancer, as each of them was associated with a significantly reduced frequency of ER+PR+ breast cancers but had no influence on that of ER-PR- cancers (Ursin & Bernstein 2005). In ovarian cancer the reproductive risk factors remained statistically insignificant in each histological subtype as has also been reported previously (Titus-Ernstoff et al. 2001, Risch et al. 1996, Kvåle et al. 1988b, Adami et al. 1994).

Our studies also demonstrated that women contracting breast cancer during premenopausal years or older than 30 years are at an increased risk of advanced stage disease. Similar results have also been obtained elsewhere (Wohlfahrt et al. 1999a).

5.3 SMRs of nongynaecological cancers, diseases and violent causes

The overall SMR of GM women (0.95, 95% CI 0.94–0.95) was low, whereas for GGM (1.01, 95% CI 0.93-1.08) it was practically the same as the national average.

The lowered SMRs of all neoplasm of GM or GGM women (Table 7) were higher than the respective SIR (0.80, 95% CI 0.78-0.81).

The SMR of bladder cancer was decreased by 41% (Table 7), whereas that of kidney cancer was increased by 38% (Table 8). The SMR of cancer in the larynx, trachea, bronchus and lung of GM women was 20% smaller than the national average (Table 7). The SMR of colon, lip, oral cavity and pharynx, oesophagus and pancreas cancer was also tendentiously decreased, whereas liver and intrahepatic bile duct cancers tended to increase among GM women (Table 7, 8). A low number of cancer cases prevents a rational SMR survey among GGM women (Table 7, 8).

<table>
<thead>
<tr>
<th>Site of cancer (ICD 10)</th>
<th>GM women</th>
<th>GGM women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs</td>
<td>SMR</td>
</tr>
<tr>
<td>All neoplasm (C00-C97)</td>
<td>5010</td>
<td>0.89</td>
</tr>
<tr>
<td>Lip, oral cavity and pharynx (C00-C14)</td>
<td>46</td>
<td>0.80</td>
</tr>
<tr>
<td>Oesophagus (C15)</td>
<td>78</td>
<td>0.87</td>
</tr>
<tr>
<td>Colon (C18, 19)</td>
<td>329</td>
<td>0.91</td>
</tr>
<tr>
<td>Pancreas (C25)</td>
<td>424</td>
<td>0.99</td>
</tr>
<tr>
<td>Larynx, trachea, bronchus and lung (C32-C34)</td>
<td>391</td>
<td>0.80</td>
</tr>
<tr>
<td>Skin, malignant melanoma (C43)</td>
<td>57</td>
<td>0.82</td>
</tr>
<tr>
<td>Bladder (C67)</td>
<td>33</td>
<td>0.59</td>
</tr>
<tr>
<td>Liver and intrahepatic bile ducts (C22)</td>
<td>4</td>
<td>0.82</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Site of cancer (ICD 10)</th>
<th>GM women</th>
<th>GGM women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs</td>
<td>SMR</td>
</tr>
<tr>
<td>Liver and intrahepatic bile ducts (C22)</td>
<td>162</td>
<td>1.08</td>
</tr>
<tr>
<td>Kidney (C64)</td>
<td>244</td>
<td>1.38</td>
</tr>
<tr>
<td>Colon (C18,19)</td>
<td>16</td>
<td>1.38</td>
</tr>
<tr>
<td>Pancreas (C25)</td>
<td>19</td>
<td>1.36</td>
</tr>
</tbody>
</table>

Mortality for endocrine and metabolic diseases was increased in GM and GGM women (Table 9). The SMR of diabetes mellitus of GGM women was nearly double compared to the national average. Mortality for different diseases of the circulatory system was also significantly increased in both groups, but it appeared in an accentuated form in GGM women. Fatal land traffic accidents were 17% more common in GM women than the national average.

Mortality for dementia and Alzheimer diseases and other disease of the nervous and sense organs was decreased in both groups, but significantly only in GM women (Table 10). The SMRs of diseases of respiratory and genitourinary systems, tuberculosis, other infectious diseases and alcohol related diseases and accidental poisoning by alcohol, suicides and sequelae of intentional self harm were about 20-40% lower than the national average in GM women. Pneumonia, the most common disease of the respiratory system in our population, was clearly a less frequent cause of death in GM women than the national average, while asthma and influenza only tended to be lowered. The SMR of diseases of the digestive system was also only tendentiously smaller than the average.
Table 9. Diseases and traffic accidents of GM and GGM women with increased SMR (1974-2001).

<table>
<thead>
<tr>
<th>Cause of death (ICD 10)</th>
<th>GM women</th>
<th>Obs</th>
<th>SMR</th>
<th>95%CI</th>
<th>GGM women</th>
<th>Obs</th>
<th>SMR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine, nutritional and metabolic diseases (E00-E90)</td>
<td>455</td>
<td>1.35</td>
<td>1.22-1.47</td>
<td>17</td>
<td>1.59</td>
<td>0.93-2.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (E10-E14)</td>
<td>424</td>
<td>1.42</td>
<td>1.29-1.55</td>
<td>17</td>
<td>1.81</td>
<td>1.06-2.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diseases of the circulatory system (I00-I425, I427-199)</td>
<td>9376</td>
<td>1.06</td>
<td>1.03-1.07</td>
<td>323</td>
<td>1.21</td>
<td>1.08-1.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart diseases (I20-I25)</td>
<td>5494</td>
<td>1.10</td>
<td>1.08-1.13</td>
<td>192</td>
<td>1.28</td>
<td>1.11-1.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular diseases (I60-I69)</td>
<td>2477</td>
<td>1.03</td>
<td>0.99-1.06</td>
<td>86</td>
<td>1.18</td>
<td>0.94-1.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Land traffic accidents (ICD 10, code 42)</td>
<td>211</td>
<td>1.17</td>
<td>1.02-1.33</td>
<td>7</td>
<td>1.14</td>
<td>0.46-2.34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 10. Diseases and violent events of GM and GGM women with decreased SMR (1974-2001).

<table>
<thead>
<tr>
<th>Cause of death (ICD 10)</th>
<th>SMR GM</th>
<th>Obs</th>
<th>SMR</th>
<th>95%CI</th>
<th>SMR GGM</th>
<th>Obs</th>
<th>SMR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious and parasitic diseases (A00-B99,J65)</td>
<td>150</td>
<td>0.82</td>
<td>0.69-0.95</td>
<td>2</td>
<td>0.34</td>
<td>0.04-1.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculosis (A15-A19,B90, J65)</td>
<td>49</td>
<td>0.60</td>
<td>0.45-0.79</td>
<td>1</td>
<td>0.39</td>
<td>0.01-2.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia and Alzheimer disease (F01,F03,G30,R54)</td>
<td>631</td>
<td>0.78</td>
<td>0.72-0.84</td>
<td>17</td>
<td>0.78</td>
<td>0.45-1.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other diseases of the nervous system and sense organs (G00-G29,G31.0-G311,G31.8-G620,G622-G720, G722-H95)</td>
<td>282</td>
<td>0.77</td>
<td>0.68-0.86</td>
<td>7</td>
<td>0.57</td>
<td>0.23-1.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other heart diseases (I30-I425,I427-152) exl. rheumatic heart diseases *</td>
<td>665</td>
<td>0.91</td>
<td>0.84-0.98</td>
<td>19</td>
<td>0.88</td>
<td>0.53-1.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diseases of the respiratory system (J00-J64, J66-399)</td>
<td>851</td>
<td>0.80</td>
<td>0.75-0.85</td>
<td>21</td>
<td>0.66</td>
<td>0.41-1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia (J12-J18,J849)</td>
<td>469</td>
<td>0.77</td>
<td>0.70-0.83</td>
<td>10</td>
<td>0.57</td>
<td>0.27-1.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis and emphysema (J40-J44, J47)</td>
<td>180</td>
<td>0.76</td>
<td>0.66-0.87</td>
<td>4</td>
<td>0.52</td>
<td>0.14-1.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diseases of the genitourinary system (N00-N99)</td>
<td>195</td>
<td>0.85</td>
<td>0.73-0.96</td>
<td>144</td>
<td>0.69</td>
<td>0.58-0.80</td>
<td>1</td>
<td>0.12</td>
</tr>
<tr>
<td>Alcohol related diseases and accidental poisoning by alcohol (F10,G312,G4051, G621,G721,I426, K292, K70, K8600,0354,P043,X45)</td>
<td>144</td>
<td>0.69</td>
<td>0.58-0.80</td>
<td>1</td>
<td>0.12</td>
<td>0.00-0.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicides and sequelae of intentional self-harm (X60-X84, Y870)</td>
<td>173</td>
<td>0.57</td>
<td>0.48-0.65</td>
<td>3</td>
<td>0.26</td>
<td>0.05-0.76</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* other heart diseases than those in Table 9.

5.3.1 Comments

The effect of multiple pregnancies on the overall and cause-specific mortality was investigated in this study for the first time on a national basis. A significantly decreased overall mortality of GM women (5% lower than expected) is in line with previous results from a study conducted in four Norwegian counties and presenting only 137 deaths among GM women (Kvale et al. 1994). In three British studies, the overall SMR of
parous women has been bigger than expected (Beral 1985, Green et al. 1988, Grundy et al. 2005). It is difficult to compare these studies, because study designs, socioeconomic circumstance and reference populations have been different. Furthermore, we could extend our investigations of the long-term effects of childbearing to a relative large GGM population with 625 deaths. The overall SMR in this group was exactly the same as the national average, i.e. higher than in GM women. This difference indicates that the physical and psychic burdens and stress of GGM women are significantly bigger than those of GM women. A markedly increased SMR in cardiovascular diseases and diabetes mellitus is also strong evidence for this assumption. It this context, special attention should be paid to the linear increase in the bodyweight of GGM women (Table 1) and associated risks.

The SMRs of all malignant neoplasm of GM and GGM women were smaller than in Norwegian (SMR 0.97 for GM women) (Kvåle et al. 1994) and English studies (SMR 0.97) (Green et al. 1988). In the Norwegian study the incidence of cervical cancer and lung cancer were much bigger than here (Kvåle et al. 1994). In the English study the SMR of cervical cancer was also bigger than in the present study, but the SMR of kidney cancer smaller (Green et al. 1988). In the present results, 90% of the protection is owing to a strong reduction in the SMR of breast, endometrial and ovarian cancers. They were responsible for 60% of the decreased overall SMR resulting in a deficit of 949 deaths of GM women.

GM women smoke less than the average population (Stakes, 2002). The SMRs of diseases, at least partly caused by smoking like lung and bladder cancers and respiratory tract diseases, were significantly low in the Finnish GM population. The SMRs of respiratory tract diseases (1.24, 95% CI 0.99-1.56), bronchitis and emphysema (1.73, 95% CI 0.95-3.15) were increased in Norway (Kvåle et al. 1994), very likely because Norwegian women smoke more than Finnish women (Pukkala et al. 2001). The possible role of hormones is worth recognising, because there are gender differences in the incidence of lung cancer (Caracta 2003), and oestrogen possibly participates in lung cancer development (Siegfried 2001).

The SMR of kidney cancer was significantly high in GM women. Such an observation has also been made in a Swedish study, where GM women had an OR of 1.91 (95% CI 1.40-2.62) compared to nulliparous women (Lambe et al. 2002). There might not only be the hormonal factors but also obesity and hypertension, which predispose to this cancer (Chow et al. 1995, Mellemgaard et al. 1994). Obesity and hypertension are also typical of GM women (Juntunen et al. 1997, Ramsay et al. 2002). Bladder cancer is said to be hormone dependent (Reid et al. 1984). However, cigarette smoking may be the most important risk factor (Pelucchi et al. 2002). It is likely that smoking and hormonal factors would act in different ways in the pathogenesis of bladder and kidney cancer (Concolino et al. 1993, Reid et al. 1984). There is also a study which supports present bladder cancer results after adjustment for age, tobacco use and previous bladder infection (Cantor et al. 1992).

Several studies have shown that multiparity is associated with an increased risk of diabetes and other metabolic diseases (Ramsay et al. 2002), coronary heart diseases (Ness et al. 1993, Ness et al. 1994, Humphries et al. 2001) and strokes (Qureshi et al. 1997) as was comprehensively documented also in this and other studies (Beral 1985, Green et al. 1988). The present SMR for diabetes mellitus would be much higher than that in the
Norwegian study (SMR 1.01, 95% CI 0.56-1.40), if the Norwegian results were approximated comparable with our findings (Kvåle et al. 1994). The SMRs of circulatory system and ischemic heart diseases are not far from each other in these studies: the present SMR 1.22 (95% CI 1.13-1.32) and the Norwegian SMR 1.11 (95% CI 0.99-1.25) (Kvåle et al. 1994). There is evidence that the number of children is directly associated with the body mass index and the waist-hip ratio, diabetes and triglycerides but inversely with HDL (Lawlor et al. 2003, Humphries et al. 2001). Even there might be confounders like life habits and socioeconomic factors which affect the development of metabolic and cardiovascular diseases. Hormonal factors may also have a direct and/or indirect influence on the risk of these diseases (Sattar & Greer 2002).

The role of hormones in neuroprotection is unclear (Garcia-Segura et al. 2001). GM women had a decreased SMR for Alzheimer diseases and other diseases of sense and nervous organs. The pathways of hormonal actions are unknown (Hogervorst et al. 2000), but as concerns the low SMR for suicides, a big family keeps mothers continuously physically and mentally active, which might prevent the brain and nervous system from degeneration. Present findings also support the theory of Durkheim (1951) (Durkheim 1951), that parenthood would give protection against suicide. Factors which have a role in these kind of accidental deaths might rather be social than hormonal (Grundy & Tomassini 2005, Roos et al. 2005, Qin & Mortensen 2003, Isometsä et al. 1996).

The majority of GM women in Finland are married (Stakes 2002). Studies from Finland and Sweden demonstrated that married mothers who are employed had the best health, whereas the income status had only a small effect on this patterning (Roos et al. 2005). In Finland, the allowance and other social benefits offered by the State for each child has guaranteed possibilities for a good standard of life, even for GM families. About 50% of GM women worked actively outside the home and 50% were housewives. The respective proportions in the general female population were 75%, and 18% (Stakes 2002). As regards the overall mortality, our findings are opposite to the results of the investigation by Grundy et al. (2005), which pointed out that nulliparous women and women with five or more children had a significantly higher mortality than other women.
6 General discussion

This study on Finnish GM women was aimed to give further information about the importance of reproductive factors in the aetiology of gynaecological cancers, and to clarify the long term consequences of multiple pregnancies with mortality figures. Good register systems, necessary for this kind of research, are available in Finland on a national basis. This fact emphasises the reliability of the present findings. Another advance is the large size and homogenous quality of the study population. In our study the results of GM women were compared to the respective national averages, whereas in most previous studies nulliparous women served as controls. This difference prevented direct comparison of our results with results of other studies. In addition, there is a significant lack of previous comparable studies with a sufficient number of GM women.

The most striking findings in this study were the significantly decreased SIRs in breast, endometrial and ovarian cancer of GM women (by 44, 43 and 36%, respectively) and GGM women (by 50, 57 and 53%, respectively) and only a slightly increased cervical cancer risk of GM women (by 17%), while the risk of GGM women was lowered (by 13%). The number of GGM women is too low for statistical evaluation of the significance of differences between GM and GGM women. Low numbers of cervical cancer cases and the low SIR in this population are expected findings, because cervical cancer incidence in Finland has been very low for several decades. Nationwide well-organised services aimed at early detection and eradication of premalignant and malignant cervical lesions have also worked very effectively among this population (Anttila et al. 1999), even though the incidence of cervical cancer among young women has slightly increased during the few past years parallel to the increase in the occurrence of cervical HPV 16 infections (Anttila et al. 2000, Laukkanen et al. 2003).

Breast cancer is the most common cancer of women in Finland; the second one is endometrial cancer and the sixth one ovarian cancer (Finnish Cancer Registry, 2005). They all are hormone dependent cancers (Key 1995). The present results showed that the effects of parity and other reproductive factors on gynaecological cancers varied greatly. In breast cancer parity was a significant risk factor, and its protective effect increased until the eighth birth. Young age at first birth was another independent risk reducer, and its effect was weaker in premenopausal than postmenopausal GM women. The risk to contract advanced breast cancer was increased in cases diagnosed during premenopausal
years and in cases with old age at first birth. The present findings support the hypothesis that the degree of breast cancer risk is dependent on the degree of pregnancy-induced differentiation of breast; maturation diminishes the risk. The differentiation is a result of the complex interaction of ovarian, pituitary and placental hormones, which induce inhibition of cell proliferation, down regulation of oestrogen and progesterone receptors and other effects. (Russo & Russo 2000, Russo et al. 2001a, Russo et al. 2001b, Russo & Russo 2001c.)

In endometrial cancer, increasing parity, older age at first birth, a long birth period and a short delivery-free period before the menopause significantly reduced the risk. It is likely that the parity-dependent decrease in endometrial cancer risk of postmenopausal GM women is due to the several times repeated long-term antiestrogenic endometrial influences of progesterone (Preston-Martin et al. 1990, Brinton et al. 1992). Even there is no firm hypothesis of how childbearing lowers endometrial cancer risk and why older age at last birth is protective, Lambe et al (1999) speculated that birth might not only affect risk by hormonal influences, but also by mechanical exfoliation.

The SIR was low in ovarian cancer. The increase in parity from the fifth birth upwards did not provide any additional protection to that obtained by five births. Similar results have also been recorded previously (Albrektsen et al. 1996, Riman et al. 2004). The incessant ovulation theory is widely accepted to explain the origin of epithelial ovarian cancer (Fathalla 1971). Ovulations during the age of 20-29 years carry the greatest risk (Purdie et al. 2003). Our findings support this theory, because GM women are in anovulation for a longer time than the average population during the most critical years. High levels of FSH and LH might also stimulate malignant transformation of ovarian epithelial cells (Cramer & Welch 1983). Because LH and FSH levels are virtually undetectable throughout pregnancy (Yen et al. 1999c), repeated pregnancies would also with this mechanism participate in the process diminishing the risk of this malignancy among GM women

Young age at first birth played a significant role in the aetiology of cervical cancer. In this age category the HPV16 and seroprevalence of C. trachomatis was also high (Study IV). Several pregnancies may induce pathological changes in the metaplastic transformation zone in the ectocervix, an area which turns out to be especially susceptible to viral and other carcinogenetic agents in this way among GM women (Nair & Pillai 1992).

Our study was also aimed to find out the effects of multiple pregnancies on the overall and cause specific mortality of GM women. The most important finding was the significantly lowered mortality of GM women. In the population of 89,922 GM women there were 18, 870 deaths, 5% less than expected (deficit 949). Comparable results have also been obtained in Norway in a much smaller population (Kvåle et al. 1994), but not in England (Beral et al. 1985, Green et al. 1988). The diseases with the biggest protective effect on the overall SMR were breast (354 deaths less than expected), endometrial (59) and ovarian (133) cancer. In cervical cancer there were 11 deaths more than expected. Cardiovascular diseases (491 more than expected) and diabetes mellitus (125) were responsible for the major part of the excess deaths of GM women.

In a recent study, the risk of breast cancer increased along with increasing placental weight. The investigators considered that pregnancy hormones are important modifiers of subsequent maternal breast cancer risk. However, in women younger than 30 years at first
birth, placental weight associated risk did not exist (Cnattingius et al. 2005), possibly because of the start of breast’s differentiation at an optimal age. The lowered breast cancer risk of women with young age at first birth with this and other mechanisms is a strong argument to recommend founding a family earlier than is the case today.

As regards cardiovascular diseases and diabetes mellitus, their increased frequency and mortality among GM women and GGM women call for attempts to diminish these risks. There is one common aetiological factor for cardiovascular diseases and diabetes mellitus, obesity, which requires special attention. Increase in the body weight is in linear correlation to the number of births (Table 1) (Juntunen et al. 1997, Sattar & Greer, 2002). Leaders and workers in the Finnish health care organisations should recognise this association and consequent long term harm and initiate adequate measures, e.g. a well-planned campaign against pregnancy-associated weight increase through education and prospective programmes would be useful and recommendable.

It is also important to recognise that deaths from dementia, suicides and alcohol related diseases and accidents were significantly rare among GM women. This finding emphasises the positive consequences of this kind of lifestyle with children in the modern world.

Our study has advantages and disadvantages. The results are based on data from three reliable Finnish national registers. However, it was not possible to get detailed individual data of GM women. Therefore, the role of confounding factors, e.g. gynaecological operations, lifestyle, usage of hormones medications etc., could not be evaluated. However they either did not differ significantly between study and control subjects or they strengthened, rather than weakened the significance of the results. The possibility of the so-called ‘healthy workers’ - effect cannot be excluded. Women with a big family may be primarily provided with better health quality properties than the average, e.g., they have optimal fertility.

The spectrum of diseases and causes of death of GM women differs greatly from that registered in the national average. The most public cause of death last year was breast cancer, second alcohol causes and accidents among working aged (15-64 years old) Finnish women (Statistics Finland 2004). In terms of health aspects, the prognostic prospects of women will not be worsened by births of several children.
7 Conclusions

1. The SIR of gynaecological cancers, updated until 2002, was significantly decreased in breast, endometrial and ovarian cancers, but increased in cervical cancer among GM women compared to the national average. The results demonstrate that grand multiparity diminishes the risk of breast, endometrial and ovarian cancers. Well-organised PAP screening testing well explains why the risk of cervical cancer of GM women was only slightly increased.

2. In breast cancer and endometrial cancer, the increase in the protective effect of pregnancies extended up to the eighth birth, but in endometrial cancer only in GM women contracting cancer after the menopause. In ovarian cancer, increasing parity from the fifth birth onwards does not give any further protection. Parity was a risk variable in cervical cancer, but an increase in parity from five to more than eight births did not significantly change the RR. Early age at first birth was protective in breast cancer, but it increased the risk in endometrial and cervical cancer. Ovarian cancer had no dependence on age at first birth in this population. Lobular and ductal cancers differed from each other in their dependence on reproductive risk factors. Increase in parity had a protective effect on ductal and shortening of the birth interval on lobular breast cancer. Premenopausal GM women had a 1.3-fold increased risk of getting an advanced breast cancer. The birth period was an important variable in endometrial cancer; the longer the period, the smaller was the cancer risk. The short premenopausal delivery free period was also advantageous. The results clearly indicate that each of these hormone dependent cancers is very specific in its relationships to reproductive variables. In cervical cancer, parity and infectious agents are important and independent risk factors, although their internal relationship in this study could not be specified.

3. The overall SMR was slightly lower than national average in GM women but equal to that in GGM women. The SMR was low in breast, endometrial and ovarian as the respective SIR figures predicted and also in dementia, alcohol related diseases and suicides. The SMR was increased in cervical cancer as expected and unexpectedly in kidney cancer. The GM women and even more the GGM women had increased mortality in cardiovascular diseases, stroke and metabolic diseases especially diabetes mellitus.
Grand multiparity has a lifelong effect on women’s health after the childbearing period. Some effects manifest themselves through long-term changes induced by hormonal factors. Some are caused by the influences of gravidity itself, for example weight gain. There are confounding factors, e.g. social variables, which may have an influence on GM women’s health in many ways, but their significance remained open in this study. GM women should be under good health control in maternal and other health care centres, not only during their pregnancies, but also for long time afterwards, because overweight often persistently remains as a severe risk factor. The follow-up of the health of GM women after the childbearing years could possibly lead to actions counteracting the development of cardiovascular diseases and diabetes mellitus and their consequent complications.

Present results demonstrate comprehensively for the first time that in a country with high quality health care organisation and sufficient socioeconomic support, grand multiparity does not increase the risks of death higher than the national average. GM women’s mortality is in fact lower than average, while the cause specific mortality figures were different as compared to the respective average recordings of Finnish women.
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Original publications


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INCIDENCE OF GYNAECOLOGICAL CANCERS AND OVERALL AND CAUSE SPECIFIC MORTALITY OF GRAND MULTIPAROUS WOMEN IN FINLAND