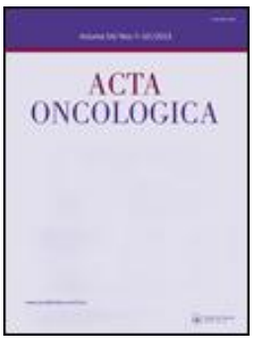

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ORIGINAL ARTICLE

Incidence of cancer among grand multiparous women in Finland with special focus on non-gynaecological cancers: A population-based cohort study

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ABSTRACT

Background. Many studies have previously revealed evidence of an association between grand multiparity (five or more deliveries) and gynaecological cancer. Oestrogen has an impact on cancer formation and the amount of circulating oestrogen is significantly higher during pregnancy. Also the lifestyle of grand multiparous women differs somewhat from the average population. Considering these factors it is plausible that also non-gynaecological cancers are associated with multiparity. The aim of our study was to determine cancer incidence among grand multiparous women, with special attention to non-gynaecological cancers.

Material and methods. All 102 541 women alive in 1974–2011 and having had at least five deliveries were identified in the Finnish Population Register and followed up for cancer incidence through the Finnish Cancer Registry to the end of 2011. Standardised incidence ratios (SIRs) were defined as ratios between observed and expected numbers of cases, the latter ones based on incidence in the entire Finnish female population.

Results. The overall incidence of non-gynaecological cancers was the same as in the reference population (SIR 0.98, 95% confidence interval 0.90–1.06). The incidence of cancers of the gall-bladder (SIR 1.42, 1.26–1.58), biliary tract (1.19, 1.04–1.35) and kidney (1.22, 1.14–1.31) was increased. There were significantly fewer cases than expected of urinary bladder cancer (SIR 0.70, 0.61–0.78), lung cancer (0.87, 0.81–0.92), colon cancer (0.94, 0.89–0.99) and all types of skin cancers. As a consequence of the decreased incidence of gynaecological cancers (SIR 0.74, 0.71–0.77) and breast cancer (0.60, 0.58–0.61), the SIR for cancer overall was 0.84 (0.83–0.85).

Conclusion. The study demonstrated that grand multiparous women have a similar overall risk of non-gynaecological cancers as other women, despite significant differences in some specific forms of cancer.

A multitude of studies have previously revealed strong evidence of an association between grand multiparity (five or more deliveries) and gynaecological cancer. Grand multiparous (GM) women are known to have decreased incidence of endometrial, ovarian and breast cancer, while the incidence of cervical cancer may be increased [1–4]. Pregnancies and breast feeding periods are a dominant part of the reproductive life of GM women, who therefore differ markedly from other women as regards lifestyle and hormonal environment. Oestrogen receptors are widely distributed in mammalian tissues and present the first step in a pathway where oestrogen affects malignant transformation, i.e. through DNA damage [5]. New evidence further shows that oestrogen has an impact on carcinogenesis in general [6], and also specifically, i.e. colon, thyroid and lung cancer have been shown to be influenced by sex steroids [7–9].

The risk of cancer is greatly dependent on lifestyle factors, which may in many ways be different in

This study is one of the largest ever done on cancer incidence among grand multiparous women and provides valuable information about the effects of multiple pregnancies on women's cancer risk.

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multiparous and other women. For instance, mortality from ischaemic heart disease and diabetes appears to be elevated among Finnish GM women [1–4,10]. Nevertheless, the incidence of non-gynaecological cancers in GM women has not been studied to a great extent. The findings on risks of non-gynaecological cancers are not consistent but there are scattered observations on significantly decreased or increased incidence of several cancer types. For example, a Taiwanese study observed [7] 28% decreased risk for colon cancer among women with four or more deliveries as compared to women with only one delivery, while a recent Egyptian study observed an odds ratio (OR) as low as 0.3 (0.1–0.5) for colorectal cancer among women with seven reported pregnancies compared with women who reported 1–3 deliveries [11]. In a meta-analysis by Dietrich et al. [12] the risk for bladder cancer among ever parous women was one third lower than among nulliparous women, and the OR for GM women was 0.74, although with a rather wide CI (0.35–1.57). In a Chinese study [13] the risk for gall bladder cancer was increased for women with five deliveries as compared with women with one delivery (OR 2.20, 95% CI 1.01–4.66). In a cohort study by Kabat et al. the risk for renal cancer increased with increasing parity and HR for GM women was 2.41 (95% CI 1.27–4.59) compared to nulliparous women [14].

The aim of this study was to obtain more information on the long-term risks and benefits of multiple pregnancies. A secondary aim was to update the results related to gynaecological cancers among the Finnish GM population reported about 10 years ago [1–4].

Material and methods

The study cohort consisted of all Finnish women having their fifth child before 2011, and who had not emigrated or died before 1974. The cohort was drawn from the Finnish Population Register, and consisted of 104 896 women. Those born abroad (n = 2355) were excluded because the data on their parity history may be unclear. Thus the final size of the cohort was 102 541 women.

For calculation of person-years of follow-up the starting point was 1 January 1974 or birth of the fifth child, whichever came later, and the end-point was the date of emigration or death, or 31 December 2011, whichever occurred first. The total number for person-years of follow-up was 2 672 587 (Table I). The follow-up could not start before 1974 because the mother-child links in the Finnish population register were not created if the mother had died before October 1973.

Information on cancer cases in the cohort was obtained from the national population-based Finnish Cancer Registry, using record linkage based on personal identity codes. The cancer cases were classified according to the main topographic categories, using the ICD-10 classification system (Table II).

Table I. Number of women (N) and person-years in the GM-cohort in each age group, follow-up period and listed according to age at first birth. The numbers in N column refer to the age in the beginning of follow-up. The respective numbers of person-years refer to the dynamic age during follow-up (i.e. a woman may contribute person-years to several categories).

	years	N	Person-years
Age at follow-up	20–29	8 940	19 140
	30–39	35 134	217 805
	40–49	34 556	493 342
	50–59	21 296	667 342
	60–69	2 614	645 106
	70–79	1	459 789
	80+	–	170 063
Time since fifth delivery	0–4.99	42 201	180 921
	5–9.99	14 276	201 152
	10+	46 064	2 290 513
Age at first birth	<20	20 364	518 453
	20–25	53 264	1 421 398
	26–29	22 961	591 576
	30+	5 952	141 160

The expected numbers of each cancer type were calculated by multiplying the number of person-years of the GM women in each five-year age category and calendar period (1974–1980, 1981–1987, 1988–1993, 1994–1999, 2000–2005, 2006–2011) by the cancer incidence rate among all Finnish women in the same age and calendar time category. SIRs were defined as the ratios between the observed and expected numbers of cases. Confidence intervals (CIs) for the SIRs were based on the Poisson distribution of the observed number of cases. The analyses were further stratified according to age at follow-up (20–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years and 80 years or older) age at first birth (<20 years, 20–24 years, 24–30 years and 30 years or older) and time since fifth birth (0–4.99 years, 5–9.99 years and 10 years or longer).

Results

During the follow-up period 16 322 cancers were diagnosed in the GM cohort.

Of the non-gynaecological cancers (Table II), significantly decreased SIRs were observed for lung cancer (SIR 0.87, 95% CI 0.81–0.92), bladder cancer (SIR 0.70, 95% CI 0.61–0.78) and cancer of unknown origin (0.62, 95% CI 0.55–0.68). The rates for all types of skin cancer were also significantly decreased. The risk of skin melanoma was especially low during the first 10 years after the fifth birth (SIR 0.38, 95% CI 0.21–0.63).

Table II. Observed (OBS) and expected (EXP) numbers of non-gynaecological cancer cases, and standardized incidence ratios (SIR) with 95% confidence intervals (CI), among grand multiparous women in Finland 1974–2011, by site.

ICD-10	Site	OBS	EXP	SIR	95% CI
	All sites	16 322	19 417	0.84	0.83–0.85
	All sites, excluding breast cancer and gynaecological cancers	11 144	11 402	0.98	0.90–1.06
C00	Lip	70	66	1.07	0.83–1.35
C01–02	Tongue	55	70	0.79	0.59–1.02
C03–06	Mouth, other	73	73	1.00	0.78–1.25
C07–08	Salivary glands	41	42	0.97	0.69–1.31
C09–14	Pharynx	30	36	0.82	0.56–1.17
C15	Oesophagus	147	162	0.91	0.77–1.06
C16	Stomach	746	731	1.02	0.95–1.09
C17	Small intestine	69	63	1.10	0.85–1.39
C18	Colon	1180	1257	0.94	0.89–0.99
C19–21	Rectum, rectosigmoid, anus	684	713	0.96	0.89–1.03
C22–24	Liver, gallbladder and biliary tract	696	563	1.24	1.06–1.42
	Liver	183	172	1.06	0.91–1.22
	Gallbladder	294	207	1.42	1.26–1.58
	Intra- and extrahepatic bile ducts	219	184	1.19	1.04–1.35
C25	Pancreas	830	809	1.03	0.96–1.09
C26	Other digestive organs	71	65	1.09	0.85–1.37
C30–31	Nose, sinuses	29	30	0.96	0.65–1.38
C32	Larynx, epiglottis	32	26	1.23	0.84–1.73
C33–34	Lung, trachea	888	1019	0.87	0.81–0.92
C40–41	Bone	21	21	1.02	0.63–1.55
C43	Skin melanoma	395	527	0.75	0.68–0.82
C44	Skin, squamous cell carcinoma	647	721	0.90	0.83–0.96
C45	Mesothelioma	29	37	0.78	0.52–1.11
C46	Kaposi sarcoma	7	10	0.68	0.27–1.40
C47	Autonomic nervous system	2	5	0.38	0.04–1.32
C48–49	Soft tissues	124	127	0.98	0.81–1.15
C64–65	Kidney	781	638	1.22	1.14–1.31
C66–68	Bladder, ureter, urethra	244	349	0.70	0.61–0.78
C69	Eye	52	51	1.06	0.80–1.38
C70–72, D32–33, D42–43	Brain, central nervous system	702	751	0.93	0.87–1.00
C73	Thyroid gland	436	334	1.31	1.19–1.43
C74–75	Other endocrine glands	25	18	1.37	0.88–2.01
C76, C80	Cancer of unknown origin	354	574	0.62	0.55–0.68
C81	Hodgkin lymphoma	48	56	0.86	0.63–1.13
C82–85, C96	Non-Hodgkin lymphoma	708	727	0.97	0.90–1.04
C90	Myeloma	315	299	1.05	0.94–1.17
C91–95	Leukaemia	394	399	0.99	0.89–1.08
	Not included above				
	Basal cell carcinoma of the skin	4120	5048	0.82	0.79–0.84

Significantly increased SIRs were observed as regards cancer of the gall-bladder (SIR 1.42, 95% CI 1.26–1.58), extra- and intrahepatic bile ducts (SIR 1.19, 95% CI 1.04–1.35), kidney (SIR 1.22, 95% CI 1.14–1.31) and thyroid gland (SIR 1.31, 95% CI 1.19–1.43).

The incidences of breast cancer, endometrial cancer and ovarian cancer were markedly decreased, while that of cervical cancer was increased (Table III). Among lesions registered by the Finnish Cancer Registry but not regarded as cancers, the SIRs for in situ lesions of breast cancer and borderline tumours of the ovary were significantly below 1.0 and the SIR for precursor lesions of cervical cancers was significantly above 1.0. The SIRs increased with increasing age at follow-up. For instance, the SIRs in age category 80 + years were 0.69 (95% CI 0.62–0.76) for breast cancer, 0.80 (95% CI 0.65–0.96) for endometrial cancer, 0.85 (95% CI 0.67–1.07) for ovarian cancer and 1.45 (95% CI 1.00–2.03) for cervical cancer. The SIR for cervical cancer according to age at follow-up followed a U-shaped curve, with the lowest SIR (1.02, 0.81–1.26) in age category 60–69 years.

As regards most cancers there was no significant variation in SIRs according to age at first birth, time of follow-up since fifth birth and age at follow-up, a few exceptions were nevertheless noted. The SIR for renal cancer was high among women with low or high age at first birth (Figure 1). Similar pattern for

Table III. Observed (OBS) and expected (EXP) numbers of breast cancer and gynaecological cancer cases, and standardized incidence ratios (SIR) with 95% confidence intervals.

ICD–10	Site	OBS	EXP	SIR	95% CI
C50	Breast	3137	5265	0.60	0.58–0.61
C51–57	Gynaecological cancers	2041	2751	0.74	0.71–0.77
C53	Cervix	356	289	1.23	1.11–1.36
C54	Endometrium	864	1352	0.63	0.58–0.66
C55	Uterus, other	23	27	0.86	0.55–1.29
C56	Ovary	594	847	0.70	0.65–0.75
C51–52, C57	Other female genitals	222	235	0.95	0.83–1.07
Premalignant lesions:					
	Breast; carcinoma in situ	113	220	0.51	0.42–0.61
	Cervix cancer; precursor	419	354	1.18	1.07–1.30
	Ovary, borderline tumour	114	148	0.77	0.64–0.91

SIRs according to age at first birth was not seen in any other cancer form. Concerning stomach cancer, the overall incidence in the cohort was similar to that in the reference population, but there was a peculiarly very low risk in the follow-up period of 5–9.99 years after the fifth birth, with only one case observed versus 11.1 expected (SIR 0.09, 95% CI 0.00–0.49). In turn, a four-fold statistically significant increase in the incidence of multiple myeloma was seen during the first five-year follow-up period after the fifth birth, based, however, on only four observed cases (SIR 4.41, 95% CI 1.20–11.28), while the incidence of myeloma among GM women in later follow-up was close to that in the reference population.

Discussion

The total incidence of non-gynaecological cancer was virtually the same as in the reference population.

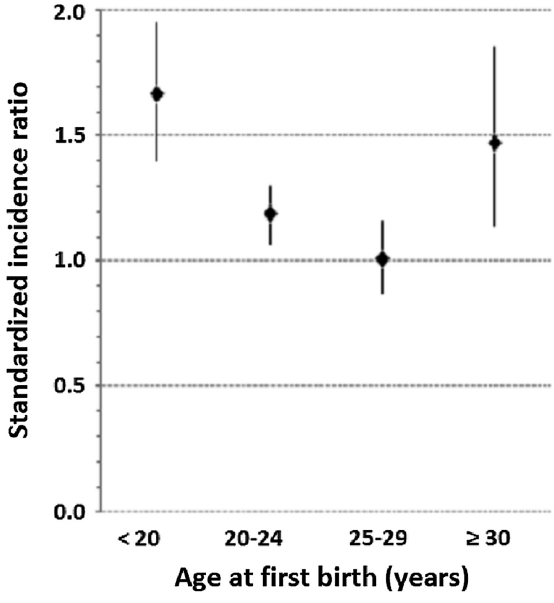

Figure 1. Standardized incidence ratio (SIR) of renal cancer, with 95% confidence intervals, according to age at first birth.

However, the incidence of some cancer types among GM women was significantly different compared with that in Finnish women in general. A decreased SIR was observed in cancers of the lung, bladder and skin, increased SIRs for kidney, thyroid, bile duct and gall-bladder. The total cancer incidence was decreased, mostly because of a decreased incidence of all gynaecological cancers and breast cancer.

This study is one of the largest GM women study ever done. It was conducted in a country with registers containing reliable data on births and cancer diagnoses. The personal identity codes given to every Finn since 1967 guarantee accurate record linkage. The reporting and diagnostic praxis is virtually the same everywhere in Finland. As we only had indirect information on lifestyle factors, our possibilities to evaluate the potential effects of confounders are incomplete.

A large part of the GM cohort belongs to the Laestadian movement within the Lutheran church in Finland, which is especially common in the northern parts of the country. Among members of the Laestadian movement the use of contraceptives is strictly forbidden, alcohol consumption is rare, but smoking is permitted. Grand multiparous women are more likely to be married than women in the reference population, and the income of Finnish GM families may be satisfactory, as an allowance is paid by the state for each child [15]. Multiple pregnancies are associated with significant weight gain followed by obesity and increased mortality from type II diabetes mellitus [10,16].

Smoking was predicted to cause 82% of all lung cancers, 25% of bladder cancers and 7% of kidney cancers of Finnish women in 2000 [17]. The low SIR for lung cancer (0.86) in this cohort fits with the fact that smoking among Finnish GM women is less frequent than among other women [18]. Although there is one observation of a decreased incidence of lung cancer among non-smoking GM women (hazard ratio 0.50, 95% CI 0.28–0.88) compared with non-smoking women with one or two children [9,19], it

appears unlikely that pregnancies could offer protection against lung cancer to any great extent.

Although smoking is an important risk factor as regards bladder cancer, more than half of the incidence is attributed to other aetiological factors [17]. The low SIR for bladder cancer (0.70) in this study and the finding by Hinkula et al. (2005) of decreased bladder cancer mortality [standardised mortality ratio (SMR) 0.59, 95% CI 0.41–0.81] [10] among Finnish GM women are so low that the decrease cannot be attributable to scarce smoking alone. The risk reduction might be explained by the hypothesis that pregnancy-related changes in sex steroids antagonise oncogenes in bladder tissue [12,20].

Besides smoking, obesity is an established risk factor of renal cancer [21]. In a previous Canadian study a BMI- and smoking-adjusted odds ratio of 2.41 (95% CI 1.27–4.59) was reported for renal cancer in GM women [14]. We also observed an increased incidence of renal cancer (SIR 1.22), but it is difficult to estimate the sum effect of the risk increasing bias due to obesity and the risk decreasing bias due to less smoking.

We observed a U-shaped curve for the relative risk of renal cancer according to age at first birth (Figure 1). The observation of an increased risk among women with first birth at a young age is in line with previous findings [22,23], but the increased risk among women with first birth at a relatively old age has not been reported before. There is some experimental evidence of an oestrogen effect in renal cancer development [24], and also evidence that physiological changes in renal function during pregnancy might affect the risk of cancer [25,26].

Despite the fact that GM women are more obese and should therefore be at an increased risk of colon cancer [27], our results demonstrate that the GM women had a slightly decreased incidence of this disease. The colonic epithelium is affected by ovarian hormones [28], but the results of large epidemiological studies have been conflicting regarding the association between colon cancer and parity. Some studies have revealed a decreased risk with increasing parity [7,29,30]. When taking the bias due to obesity into account, our SIR (0.94) may be too high and actually accord with the hypothesis of increasing parity decreasing colon cancer incidence.

In the present study we found a 37% increase in the incidence of biliary tract cancer in GM women. A Chinese study revealed an approximately two-fold increase in BMI-adjusted risk of gall-bladder cancer among GM women, while the respective risk as regards bile duct cancer was decreased [13,31]. A similar risk reduction as regards bile duct cancer was not seen in our study. Obesity and cholelithiasis are known to increase the risk of gall-bladder cancer [32,33]. High levels of endogenous oestrogens have also been associated with an increased risk [34].

We found an increased SIR for thyroid cancer in the present study. As mentioned earlier, approximately one third of the study cohort comes from the northern part of Finland, with exceptionally high diagnostic activity concerning thyroid malignancies since the 1980s, and as a consequence a higher incidence of thyroid cancer. As a result of this surveillance bias, our risk estimate for thyroid cancer may be somewhat too high. Similar surveillance bias is not likely to confound risk estimates of other cancers. High levels of oestrogens, human chorionic gonadotrophin (hCG) and thyroid-stimulating hormone (TSH) during pregnancy are responsible for direct thyroid stimulation and may promote tumour growth [35,36]. The increased risk in the first few years postpartum followed by a downward trend, as reported in several studies [37–39], was not observed in our study. One possibility is that surveillance bias affected the earlier studies.

The incidence of multiple myeloma in our study was increased during the first five years after the fifth delivery. This finding may well be due to chance, but it might also be a result of transient immune suppression during pregnancy [40].

In the present study, the SIR for melanoma was 0.75 (95% CI 0.68–0.82). Data from 10 previous studies also suggest that grand multiparity may decrease the risk of melanoma (pooled OR 0.73, 95% CI 0.51–1.04 for GM women) [41]. Sun exposure, especially sunburn, elevates the risk of melanoma [42] and it is natural that women with big families do not have much time for sunbathing. In a recent meta-analysis [43] it appeared that the negative association between parity and melanoma is confounded by socioeconomic status.

It is known that cumulative sun exposure is a predisposing factor as regards basal cell cancer and squamous cell skin cancer [44]. The overall incidence of all skin cancers is lower in the northern parts of Finland than elsewhere, which may explain the decreased risk of skin cancers. An alternative explanation for the low risk of basal cell skin cancer may be the inverse association suggested between BMI and basal cell carcinoma [45], which may be related to increased oestrogen production in adipose tissue [46].

The risk estimates for gynaecological cancers and breast cancer were not the main focus of the current study. These cancer risks have been studied in detail in connection with a similar register-based cohort and published in several papers [1–4,47,48]. The current cohort simply offers a longer follow-up period for the women in the old cohort and adds to it about 25 000 women who had their fifth child after

1997. The new analyses provide slightly higher SIRs than published earlier concerning breast (SIR 0.60 vs. 0.55 [1]), endometrial (0.63 vs. 0.57 [2]) and ovarian (0.70 vs. 0.64 [4]) cancers because of the larger fraction of person-years in the older age categories in the current follow-up. The SIRs for both breast and gynaecological cancers were all higher among the present GM women than among women with 10 or more deliveries in a recent study of ours [49], indicating that further deliveries provide further protection. A similar phenomenon – decreased cancer risk with increasing number of births – was also observed in an earlier study on Finnish GM women [1]. For cervical cancer, in opposite to other gynaecological cancers, the SIR increases with increasing parity, because its aetiology largely consists of human papilloma virus infection. Multiparity may also be an independent risk factor [3]. In our study the SIR was 1.23, i.e. higher than in the older Finnish study by Hinkula et al. (1.13 [3]), most likely caused by larger fraction of person-years in the age categories of 70 + years with SIRs 1.3 or higher.

This study, on a national cohort of 103 000 GM women, shows that these women have a lowered cancer risk, mostly as a result of low gynaecological and breast cancer rates. The results regarding most other cancer sites suggest that malignant transformation is generally not related to reproductive history and therefore there is no need to plan more intensive cancer screening procedures for GM women than for of other women. As comprehensive adjustment for cofactors, such as obesity and smoking was not possible in this study setting, further research is needed to determine the effect of grand multiparity alone on some non-gynaecological cancers.

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