

The role of pregnancy in maternal cancer risk: Epidemiologic evidence from the Nordic Countries Linked Birth and Cancer Registries Cohort Project

Rebecca Troisi¹, Ingrid Glimelius^{2,3}, Tom Grotmol⁴, Mika Gissler^{5,6}, Cari M. Kitahara¹, Anne Gulbech Ordning⁷, Solbjørg Makalani Myrvtveit Sæther⁴, Camilla Sköld³, Henrik Toft Sørensen⁷, Britton Trabert⁸ and Tone Bjørge^{4,9}

1) Division of Cancer Epidemiology and Biostatistics, National Cancer Institute, National Institutes of Health, Rockville, Maryland, USA

2) Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden

3) Department of Medicine, Clinical Epidemiology Unit, Karolinska Institutet Stockholm, Sweden

4) Cancer Registry of Norway, Oslo, Norway

5) Department of Knowledge Brokers, Finnish Institute for Health and Welfare (THL), Helsinki, Finland

6) Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden and Academic Primary Health Care Centre, Region Stockholm, Stockholm, Sweden

7) Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

8) Department of Obstetrics and Gynecology, University of Utah, Cancer Control and Population Sciences Program, Huntsman Cancer Institute at the University of Utah, Salt Lake City, Utah, USA

9) Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

Correspondence: Dr. Rebecca Troisi, 9609 Medical Center Drive, MSC 9773, Rockville, MD 20850, USA

E-mail: troisir@mail.nih.gov

ABSTRACT

The experience of pregnancy has a lasting impact, in many cases beneficial, on cancer risk in the mother. In the long term, breast, ovarian, and endometrial cancers are lower in parous women, and each pregnancy provides an additional risk reduction. Kidney cancer, in contrast, is elevated in parous women, while associations of parity with colorectal, thyroid, and pancreatic cancers are unclear. Timing of pregnancy matters, with a first birth at older ages compared with younger ages associated with an increased breast cancer risk, while endometrial and ovarian cancer risk is lower in women with an older versus younger age at last birth. Other characteristics of pregnancy are likely important but difficult to assess because of the time lag between pregnancy and cancer diagnosis, the potential for misclassification from recall in retrospective studies, and the rarity of many pregnancy conditions. Linking health-registries and pooling of data in the Nordic countries have provided an excellent opportunity to conduct epidemiologic research on rare pregnancy conditions and subsequent cancer, although legal restrictions have increasingly limited this approach. We hope that by identifying and describing associations with attributes of pregnancy, we may discover clues to the underlying biological mechanisms that lead to cancer development. Understanding the association of pregnancy and cancer risk will be of increasing importance as women have fewer pregnancies at later ages.

This is an open access article distributed under the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Over half a century ago, epidemiologic studies documented reduced breast cancer risk among parous women (1), particularly those who delivered children at an early age, compared with nulliparous women (2). More recently, studies have focused on various characteristics of pregnancy as markers for exposures that occur while the breast is vastly remodelling in structure and morphology. Shifts in child-bearing patterns (*i.e.*, having fewer children and giving birth at older ages), and rising incidence of some pregnancy complications, for example preeclampsia (3), may affect cancer risk in later life. Record linkage studies, largely from the Scandinavian countries, have successfully used data

from health and other registers to obtain exposure information over meaningful time frames. These large population-based datasets also address the relative rarity of most cancers. This brief review covers the epidemiology of pregnancy and its characteristics and subsequent maternal cancer risk (summarized in Table 1 (4)), based on findings from a Nordic-National Institutes of Health (NIH) collaboration of studies conducted in the Nordic Countries Linked Birth and Cancer Registries Cohort Project (Nordic Project), an effort that combined linked registry birth and cancer data from Denmark, Finland, Norway, and Sweden. While this is not a comprehensive review of the literature on this topic, we have tried to put the Nordic findings in the context of other major epidemiological

Table 1. Summary of pregnancy-related risk factors for selected maternal cancers.

	Breast	Colorectal	Endometrial	Ovarian
Nulliparity	↑	?	↑	↑
Parity	↓	?	↓	↓
Lactation	↓	-	-	↓
Older age at first birth	↑	?	?	↓
Older age at last birth	?	-	↓	↓
Shorter gestational length	?	?	-	↑
Fetal growth/Birth weight	?	?	?	-
Twin birth	?	?	?	-
Infant sex	-	?	?	?
Preeclampsia	↓	?	?	?

↑ decreased risk, ↓ increased risk, - no association, ? uncertain/conflicting findings

work. This large collaboration and its resulting resources provided data to explore in greater detail whether profound physiological states in pregnancy are linked with subsequent cancer risk.

REVIEW OF PREGNANCY FACTORS AND MATERNAL CANCER RISK

Breast cancer

Breast cancer, because of its higher incidence than other tumours and clear association with reproductive hormones, has been most studied regarding the influence of pregnancy. The effect of parity on the mother's breast cancer risk depends on her age at pregnancy and tumour subtype (5). For several years following delivery, there is a slight increase in breast cancer risk, mainly of estrogen receptor (ER) negative tumours. In contrast, if the pregnancy occurs at a young age, the long-term risk of ER positive tumours is reduced (reviewed in Behrens (6)). To provide benefit, the pregnancy must be full-term, as miscarriages do not provide equivalent protection (7); it has been unclear if gestational length of pregnancy resulting in live birth is inversely associated with risk (8). Pregnancy-associated breast cancer (PABC), likely from an abundance of somatotrophic hormones affecting tumour progression, is rare, but often diagnosed at an advanced stage (9).

Data from the Nordic Project (10) demonstrated, as expected, that parity was inversely associated with breast cancer risk, with an approximate 25% risk decrease for ≥ 4 births vs. 1 birth. Age at birth also was strongly associated with risk: Older age at first birth and at last birth were positively associated with risk, while time since first birth and time since last birth were inversely associated with risk. In contrast to inconsistent results for whether duration of pregnancy is associated with breast cancer risk (8), in the Nordic Project data (10), gestational length was inversely associated with breast cancer risk both for the first and last birth.

The association of the mother's weight gain in pregnancy with her later breast cancer risk is complicated by the strong correlations between maternal pregnancy weight and gestational length of the pregnancy,

the baby's birth weight, and the mother's later adult weight. Studies for the most part have been inconsistent, however, a Finnish cohort study found that pregnancy weight gain was positively associated with subsequent breast cancer risk independent of weight at diagnosis (11). Birth weight has been positively associated with maternal breast cancer risk, but there have been few studies, with findings limited to subgroups (12). We were able to assess multiple correlated variables simultaneously in the Nordic Project (10). Having had a premature first birth (<32 weeks' gestation vs. 37-41 weeks' gestation) or premature last birth was associated with a 10-15% increase in risk. Risk was reduced by approximately 20% among women with a high maternal BMI (≥ 30) compared with average BMI (18.0-24.9). The breast cancer risks were increased slightly (<10%) with low birth weight (<1500 g) for the first birth and for the last birth compared with average weight (2,500-3,499 g). In the subset of pregnancies with information on gestational age and birth weight, breast cancer risk was slightly lower for small for gestational age in the first birth and slightly higher for large for gestational age compared with appropriate size for gestational age. With simultaneous adjustment, the results for multiple births, maternal body mass index (BMI), and premature birth (for the first birth) remained the same, but the elevated risk for low birth weight (for the first birth) was attenuated.

Whether twin pregnancies are a risk factor for breast cancer is unclear, although several Scandinavian cohort studies, mainly in younger women, have found a modest risk reduction in mothers of twins compared with mothers of singletons (reviewed in 13), while results from the Nordic Project (10) showed that having delivered twins ($n=2,463$ cases) or higher-order multiples compared to singletons was associated with a <10% increase in risk.

The effects of other factors related to pregnancy or the offspring on maternal breast cancer risk also have been investigated. Offspring sex has been hypothesized to affect maternal breast cancer risk through differences in maternal hormones, but results of studies have been inconsistent (13), and there was no association in the Nordic Project (10). Despite the paucity of information on placental size, two studies have demonstrated positive associations between placental weight and diameter (14), and an inverse association with maternal floor infarctions (15) and subsequent breast cancer in the mother. Breastfeeding duration is inversely associated with breast cancer risk, with a stronger and more consistent relation for hormone receptor-negative tumours (16).

Certain pregnancy complications also may be associated with subsequent maternal breast cancer risk, for example preeclampsia, but because these conditions are rare, the investigations require large studies like the Nordic Project to reach the statistical precision required for accuracy. Several studies have shown a reduced risk of breast cancer among women with a history of

preeclampsia, a hypertensive disorder of pregnancy, compared with those with normotensive pregnancies (17). Interestingly, one study demonstrated a marked reduction with elevated mean arterial pressure (MAP) (18) and with systolic blood pressure increasing from mid- to late pregnancy below the diagnostic criterion for hypertension (*i.e.*, in normotensive pregnancies) (19). A prevailing feature of preeclampsia is anti-angiogenesis, which is also essential in restricting tumour growth, although there are several other biological hypotheses that have been posited to explain the lower breast cancer risk.

Our findings from the Nordic Project (10) were consistent with about a 10% reduction in breast cancer risk in women who developed hypertension during pregnancy, or preeclampsia. The number of cases were too few to assess severe preeclampsia or eclampsia. Breast cancer risks were similar for gestational hypertension and preeclampsia among women without pre-existing (before the pregnancy) hypertension. The results were also similar among women without pre-existing diabetes, and with further adjustment for gestational length. No other pregnancy complication including macrosomia, hyperemesis, abruptio placenta, placenta previa, antepartum haemorrhage and poor fetal growth, were associated with breast cancer risk, except for an approximate 15% increase in risk associated with retained placenta.

Further adjustment for age at first birth did not change any of the results for pregnancy complications and breast cancer risk. The associations for hypertensive conditions and breast cancer risk were similar in women who experienced preeclampsia or gestational hypertension in the first pregnancy or in a subsequent pregnancy and were similar for all three hypertensive conditions by age at breast cancer diagnosis, and time since last and first birth. Breast cancer risk appeared slightly lower for gestational hypertension among women with one live or still birth pregnancy carrying a male compared with a female fetus, but the difference was not statistically significant. Results were similar for the three hypertensive conditions by calendar year of breast cancer diagnosis (before 2002, 2002-2008 and 2009-2013). Adjusting for smoking and BMI did not affect the results in women with this information.

Colorectal cancer

Several prospective studies have evaluated the role of pregnancy in relation to colorectal cancer risk, with inconsistent results. The EPIC (European Prospective Investigation into Cancer and Nutrition) study found little evidence for associations between parity or age at first full-term pregnancy and colorectal cancer (20). On the other hand, a US study (National Institute of Health-American Association of Retired Persons Diet and Health Study) found that age at first childbirth was positively associated with colorectal cancer, while parity was inversely associated (21). A Swedish registry-based study found parity to be positively associated

with adenocarcinoma of the proximal colon (22). In a report from the Women's Health Initiative Observational Study (US), greater parity was associated with a reduced colorectal cancer risk (23). The Million Women Study (UK) reported lower colorectal cancer risk in parous than in nulliparous women, but no risk trend was observed by parity (24).

Our large population-based case-control study (25) including more than 22,000 cases within the Nordic Project found no evidence for associations between parity, age at first and last birth, and time since first and last birth and colorectal adenocarcinoma in parous women overall, by specific subsites (proximal and distal colon and rectum), or in analyses stratified by mother's year of birth, parity, and proxies for menopausal status. The study population was relatively young (mean age at colorectal cancer diagnosis was 57 years), as it was restricted to women with a prior birth recorded in national birth registries.

Future studies would benefit from the inclusion in analyses of possible confounders, such as use of exogenous hormones, obesity, alcohol, smoking, and aspirin and NSAID (nonsteroidal anti-inflammatory drug) use. Larger studies would also be valuable by allowing comparison of risks across morphologically and molecularly defined subtypes and anatomical subsites, and by taking information on colorectal cancer screening into account.

Endometrial cancer

Much of what is known about the epidemiology of uterine cancer relates to endometrial cancer, as uterine sarcomas comprise only 3-7% of uterine malignancies (26). The risk of endometrial cancer rises sharply among women in their late forties to mid-sixties and is strongly dependent on lifetime hormonal exposures. Various aspects of reproduction have been explored extensively regarding endometrial cancer.

Pregnancy is known to confer long-term protection against endometrial cancer. Conversely, nulliparity is associated with elevated endometrial cancer risk (27,28). Primary and secondary infertility are also associated with increased endometrial cancer risk, with independent effects (29). The pregnancy history of women with endometrial cancer has been examined in depth, including timing of births (27,28,30-32), twin births, and sex of offspring (33). Several studies have reported reduced risks with either older age or shorter time since last birth. Investigators have hypothesized that this reflects a protective effect of the mechanical clearance of initiated cells (27,28,30-32). However, existing studies have been unable to evaluate timing of pregnancy associations by histologic subtype (32). Birth of twin boys, but not twin girls or non-sex-concordant twins, appears to put women at increased risk of endometrial cancer (33). Pregnancy complications such as preeclampsia also have been explored in relation to endometrial cancer, with inconclusive results (34-35). Gestational diabetes has been associated with

increased risk of both endometrial hyperplasia and endometrial cancer (36).

Recent data indicate that the associations between reproductive factors and endometrial cancer differ by dualistic subtype (Types I and II) (32,37) motivating us to investigate endometrial cancer risk overall and by subtype (dualistic and histologic subtype if sufficiently powered) in relation to pregnancy-related factors, pregnancy complications, and birth characteristics in the Nordic Project (38). Pre-existing and pregnancy-related hypertensive conditions were associated with increased endometrial cancer risk (approximately 50-90%), with consistent associations across dualistic type (Type I and II). Increasing number of pregnancies and shorter time since last birth were associated with markedly reduced endometrial cancer risk, with consistent associations across most histologic subtypes. These findings support the role for both hormonal exposures and cell clearance as well as immunologic/inflammatory aetiologies for endometrial cancer.

Ovarian cancer

Epithelial ovarian cancer has the worst prognosis of all gynaecological malignancies with an approximate 45% overall 5-year relative survival rate (39). Parity is well known to be associated with decreased risk of ovarian cancer. Parous women have a 30-40% lower risk of developing ovarian cancer, and an additional protective effect is seen with increasing parity (39,40). Spontaneous or induced abortion does not seem to influence the risk of ovarian cancer (41), suggesting that a longer period of hormone exposure or anovulation is required for risk reduction. Findings from studies on pre- and post-term delivery have been inconsistent (42,43), and additional studies could shed light on the effect of pregnancy length. Other pregnancy-related factors such as high or low birth weight (42), preeclampsia (34,44), offspring gender (43,45), twin birth (43), and placental weight (46) have not been conclusively associated with ovarian cancer. Pregnancies at older ages seem to provide stronger protection against ovarian cancer than pregnancies at younger ages (39). Lactation is also protective, and the effect size increases with duration of breastfeeding (47).

The inconsistencies in previous studies led us to in-depth study associations between pregnancy and birth characteristics and risk of epithelial ovarian cancer by histologic subtype in parous women in the Nordic Project (48). Increasing number of pregnancies was associated with reduced ovarian cancer risk. The strongest risk reductions were for clear cell and endometrioid histologic subtypes, but reduced risks with increasing number of pregnancies were observed for all subtypes. We found that preterm delivery was associated with increased risk of ovarian cancer, and the shorter the pregnancy, the stronger the association. Older age at both first and last birth was associated with a decreased risk. We found no association with twin pregnancies, preeclampsia or offspring size with overall epithelial ovarian cancer risk.

While parity is an established risk factor for epithelial ovarian cancer, the association with non-epithelial ovarian tumours has not been studied. Non-epithelial ovarian cancers are divided into sex cord-stromal tumours (SCSTs) and germ cell tumours (GCTs). We investigated the associations of pregnancy characteristics by these subtypes in the Nordic Project (49). Like our findings in epithelial ovarian cancer, the risk of SCSTs, but not GCTs, decreased with older age at first and last birth. SCST risk decreased gradually with increasing age at first or last birth. A recent childbirth (shorter time since first or last birth) was also associated with decreased risk of SCSTs (but not GCTs). Number of births, preterm birth, preeclampsia, and offspring size were not associated with risk of SCSTs or GCTs. Even with population data from four countries, the number of these tumours was limited, which could explain the lack of associations. Recently, parity was found to be associated with a better prognosis for germ cell ovarian tumours, while it did not impact survival for other ovarian cancer subtypes (50).

Leukaemia/lymphoma, sarcomas, and other solid tumours

The relations between pregnancy characteristics and other malignancies have been much less investigated than breast, colorectal, endometrial, and ovarian cancers. This is likely due to the less pronounced hormonal aetiology of these malignancies and their lower incidence.

While malignant melanoma is the most common cancer arising during pregnancy, accounting for about a third of malignancies among expectant mothers, parous women are not at higher risk of subsequently developing melanoma than nulliparous women (51), or of developing non-melanoma skin cancer (52). Women have a lower incidence of leukemias and lymphomas overall than men, but there is little evidence that pregnancy factors are associated with non-Hodgkin's lymphoma (53). One study, however, showed that parous women had about a two-and-a-half-fold increased risk of lymphoid neoplasm compared with nulliparous women, but no associations were observed between lymphoid neoplasms and other reproductive factors, including age at first birth and breastfeeding (54).

Parity is unlikely to play an important role in the aetiology and disease progression of Hodgkin's lymphoma (55,56) and the focus of research is on the ability to conceive after treatment (57,58). Pregnancy-related hormonal or immunological changes seem to have only a minor influence in the aetiology of leukemias. However, one study did find a small tendency toward reduced risk of chronic myeloid leukaemia with higher parity (59) and another reported short-term protection against acute myeloid leukaemia with pregnancy (60). Risk of sarcoma was not associated with parity and number of abortions in one study (61), but another suggested an increased risk in women who were older at first birth (62).

Age at first birth, parity, and number of live births

are not consistently related to female thyroid cancer risk (63,64). Like breast cancer, thyroid cancer risk appears to be elevated in the first few years after pregnancy but not subsequently (65,66), which may indicate a promotional effect of pregnancy hormones in thyroid carcinogenesis. Diagnosis of hyperemesis gravidarum has been associated with increased risk of maternal thyroid cancer (67). Higher fetal growth and birth weight also have been associated with an increased risk of maternal thyroid cancer (68), while longer duration of breastfeeding has been associated with a modest reduction in risk (65,69). It is not clear whether any or all of these findings are confounded by healthcare access or thyroid cancer screening, leading to the identification and diagnosis of subclinical thyroid cancers (63). These issues are being addressed in data from the Nordic Project.

Meta-analyses of pancreatic cancer show a risk reduction in parous women compared with nulliparous women (70), with two children being most protective (71). Higher risk of pancreatic cancer has been associated with older age at first birth (72). In contrast, a meta-analysis demonstrated an increased risk of kidney cancer in parous compared with nulliparous women, and an increase in risk with each subsequent birth (73).

USE OF NORDIC REGISTERS IN RESEARCH

Understanding the role of pregnancy on subsequent maternal cancer risk is challenging because of a relatively long latency period between exposure and disease, the possibility of bias in recall of information about pregnancy in case-control studies based on interviews or questionnaires, and the large numbers of cases required for stable estimates when studying rare exposures or cancer types.

For several decades, the Nordic countries have collected administrative health and welfare data (74, 75), which can be leveraged in studies of pregnancy characteristics and subsequent cancer risk. Registry-based research in the Nordic countries has benefited from Personal Identification Numbers, making it possible to link various data sources, including all other registers, also for example medical records and biobank samples. This has allowed the study of rare exposures, such as eclampsia or other pregnancy complications recorded in medical birth registries or rare malignancies recorded in cancer registries.

The use of registries also has the advantage of minimizing bias. As all residents who had a birth or a cancer diagnosis in the Nordic countries are captured in the registries, selection bias introduced by including patients treated by specific hospitals or with specific insurance plans is virtually eliminated.

REFERENCES

1. Wynder EL, Bross IJ, Hirayama T. A study of the epidemiology of cancer of the breast. *Cancer* 1960; **13**: 559-601.

Standardized data from registries also eliminate bias from participant self-selection and recall. Information on perinatal factors based on mandatory reporting of birth information supplements the analysis, and while it can be missing for some variables, lack of data is unlikely to be related to subsequent cancer risk. Information on pregnancy complications especially in the early years of the birth registries is not complete, and could be misclassified, but any misclassification would tend to bias results towards the null.

CONCLUSIONS

An understanding of the origin of cancer is crucial for cancer screening, prevention, and treatment. Complex biological mechanisms promote carcinogenesis, and there is increasing evidence that pregnancy-related exposures may have long-lasting impact on health and disease susceptibility in the mother. In addition, understanding the role of pregnancy in the subsequent health of the mother is important as women are experiencing pregnancy at older ages and are having less children. This review has provided evidence that some pregnancy and pregnancy-related factors are involved in the carcinogenesis of several cancer types. The abilities to link various health registries and to pool data across the Nordic countries has provided opportunities to conduct high-quality research of pregnancy exposures and subsequent maternal cancer risk. Unfortunately, this is becoming increasingly difficult due to legal restrictions, although research can employ meta-analysis approaches in joint projects. The future should also aim to integrate biological data into these large studies, further deepening the understanding of the differences in aetiology for malignancies in reproductive organs.

The next step in increasing the utility of these resources will involve linking with other population data, such as prescription or in-vitro fertilization registers, and with biospecimens, most likely through birth cohort biobanks (76,77). The latter may lead to the identification of persistent changes in epigenetic markers that could represent pregnancy or *in utero* exposures, which could then be associated with cancer risk. These approaches could improve our understanding of potential preventable causes of cancer.

ACKNOWLEDGEMENTS

This manuscript is based on the proceedings of a meeting (4) convened by investigators participating in a project entitled, "Pregnancy characteristics and maternal cancer: A joint Nordic study" which was financially supported by the Nordic Cancer Union. The group-meeting in May 2017 was financially supported by the Journal of Internal Medicine.

2. MacMahon B, Cole P, Lin TM, Lowe CR, Mirra AP, Ravnihar B, et al. Age at first birth and breast cancer risk. *Bull World Health Organ* 1970; **43** (2): 209-221.
3. Jeyabalan A. Epidemiology of preeclampsia: Impact of obesity. *Nutr Rev* 2013; **71** (Suppl 1): 10.
4. Troisi R, Bjørge T, Gissler M, Grotmol T, Kitahara CM, Myrteit Saether SM, et al. The role of pregnancy, perinatal factors and hormones in maternal cancer risk: a review of the evidence. *J Intern Med* 2018; **283** (5): 430-445.
5. Nichols HB, Schoemaker MJ, Cai J, Xu J, Wright LB, Brook MN, et al. Breast cancer risk after recent childbirth: a pooled analysis of 15 prospective studies. *Ann Intern Med* 2019; **170** (1): 22-30.
6. Behrens I, Basit S, Jensen A, Lykke JA, Nielsen LP, Wohlfahrt J, et al. Hypertensive disorders of pregnancy and subsequent risk of solid cancer – A nationwide cohort study. *Int J Cancer* 2016; **139** (1): 58-64.
7. National Cancer Institute. Early reproductive events and breast cancer: Workshop statement. <https://www.cancer.gov/types/breast/ere-workshop-statement>. Published 2003.
8. Albrektsen G, Heuch I, Hansen S, Kvåle G. Breast cancer risk by age at birth, time since birth and time intervals between births: exploring interaction effects. *Br J Cancer* 2005; **92** (1): 167-175.
9. Schedin P. Pregnancy-associated breast cancer and metastasis. *Nat Rev Cancer* 2006; **6** (4): 281-291.
10. Troisi R, Ording AG, Grotmol T, Glimelius I, Engeland A, Gissler M, et al. Pregnancy complications and subsequent breast cancer risk in the mother: a Nordic population-based case-control study. *Int J Cancer* 2018; **143** (8): 1904-1913.
11. Kinnunen TI, Luoto R, Gissler M, Hemminki E, Hilakivi-Clarke L. Pregnancy weight gain and breast cancer risk. *BMC Womens Health* 2004; **4** (1): 7.
12. Troisi R, Doody DR, Mueller BA. A linked-registry study of gestational factors and subsequent breast cancer risk in the mother. *Cancer Epidemiol Biomarkers Prev* 2013; **22** (5): 835-847.
13. Nechuta S, Paneth N, Velie EM. Pregnancy characteristics and maternal breast cancer risk: a review of the epidemiologic literature. *Cancer Causes Control* 2010; **21** (7): 967-989.
14. Cnattingius S, Torrang A, Ekbohm A, Granath F, Petersson G, Lambe M. Pregnancy characteristics and maternal risk of breast cancer. *JAMA* 2005; **294** (19): 2474-2480.
15. Cohn BA, Cirillo PM, Christianson RE, van den Berg BJ, Siiteri PK. Placental characteristics and reduced risk of maternal breast cancer. *J Natl Cancer Inst* 2001; **93** (15): 1133-1140.
16. Islami F, Liu Y, Jemal A, Zhou J, Weiderpass E, Colditz G, et al. Breastfeeding and breast cancer risk by receptor status – a systematic review and meta-analysis. *Ann Oncol* 2015; **26** (12): 2398-2407.
17. Wang F, Zhang W, Cheng W, Huo N, Zhang S. Preeclampsia and cancer risk in women in later life: a systematic review and meta-analysis of cohort studies. *Menopause* 2021; **28** (9): 1070-1078.
18. Richardson BE, Peck JD, Wormuth JK. Mean arterial pressure, pregnancy-induced hypertension, and preeclampsia: evaluation as independent risk factors and as surrogates for high maternal serum alpha-fetoprotein in estimating breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 2000; **9** (12): 1349-1355.
19. Cohn BA, Cirillo PM, Christianson RE, van den Berg BJ, Siiteri PK. Placental characteristics and reduced risk of maternal breast cancer. *J Natl Cancer Inst* 2001; **93** (15): 1133-1140.
20. Tsilidis KK, Allen NE, Key TJ, Bakken K, Lund E, Berrino F, et al. Oral contraceptives, reproductive history and risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition. *Br J Cancer* 2010; **103** (11): 1755-1759.
21. Zervoudakis A, Strickler HD, Park Y, Xue X, Hollenbeck A, Schatzkin A, et al. Reproductive history and risk of colorectal cancer in postmenopausal women. *J Natl Cancer Inst* 2011; **103** (10): 826-834.
22. Lu Y, Oddsberg J, Martling A, Lagergren J. Reproductive history and risk of colorectal adenocarcinoma. *Epidemiology* 2014; **25** (4): 595-604.
23. Murphy N, Xu L, Zervoudakis A, Xue X, Kabat G, Rohan TE, et al. Reproductive and menstrual factors and colorectal cancer incidence in the Women's Health Initiative Observational Study. *Br J Cancer* 2017; **116** (1): 117-125.
24. Pust AB, Alison R, Blanks R, Pirie K, Gaitskell K, Barnes I, et al. Heterogeneity of colorectal cancer risk by tumour characteristics: Large prospective study of UK women. *Int J Cancer* 2017; **140** (5): 1082-1090.
25. Bjørge T, Gissler M, Ording AG, Engeland A, Glimelius I, Leinonen M, et al. Reproductive history and risk of colorectal adenocarcinoma in parous women: a Nordic population-based case-control study. *Br J Cancer* 2016; **115** (11): 1416-1420.
26. D'Angelo E, Prat J. Uterine sarcomas: a review. *Gynecol Oncol* 2010; **116** (1): 131-139.
27. Dossus L, Allen N, Kaaks R, Bakken K, Lund E, Tjønneland A, et al. Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2010; **127** (2): 442-451.
28. Karageorgi S, Hankinson SE, Kraft P, De Vivo I. Reproductive factors and postmenopausal hormone use in relation to endometrial cancer risk in the Nurses' Health Study cohort 1976-2004. *Int J Cancer* 2010; **126** (1): 208-216.

29. Yang HP, Cook LS, Weiderpass E, Adami H-O, Anderson KE, Cai H, et al. Infertility and incident endometrial cancer risk: a pooled analysis from the epidemiology of endometrial cancer consortium (E2C2). *Br J Cancer* 2015; **112** (5): 925-933.
30. Pocobelli G, Doherty JA, Voigt LF, Beresford SA, Hill DA, Chen C, et al. Pregnancy history and risk of endometrial cancer. *Epidemiology* 2011; **22** (5): 638-645.
31. Pfeiffer RM, Mitani A, Landgren O, Ekblom A, Kristinsson SY, Björkholm M, et al. Timing of births and endometrial cancer risk in Swedish women. *Cancer Causes Control* 2009; **20** (8): 1441-1449.
32. Setiawan VW, Yang HP, Pike MC, McCann SE, Yu H, Xiang YB, et al. Type I and II endometrial cancers: have they different risk factors? *J Clin Oncol* 2013; **31** (20): 2607-2618.
33. Albrektsen G, Heuch I, Thoresen S, Kvale G. Twin births, sex of children and maternal risk of endometrial cancer: a cohort study in Norway. *Acta Obstet Gynecol Scand* 2008; **87** (11): 1123-8.
34. Calderon-Margalit R, Friedlander Y, Yanetz R, et al. Preeclampsia and subsequent risk of cancer: update from the Jerusalem Perinatal Study. *Am J Obstet Gynecol* 2009; **200**: 63.e1-5.
35. Hallum S, Pinborg A, Kamper-Jorgensen M. Long-term impact of preeclampsia on maternal endometrial cancer risk. *Br J Cancer* 2016; **114** (7): 809-812.
36. Wartko PD, Beck TL, Reed SD, Mueller BA, Hawes SE. Association of endometrial hyperplasia and cancer with a history of gestational diabetes. *Cancer Causes Control* 2017; **28** (8): 819-828.
37. Yang HP, Wentzensen N, Trabert B, Gierach GL, Felix AS, Gunter MJ, et al. Endometrial cancer risk factors by 2 main histologic subtypes: the NIH-AARP Diet and Health Study. *Am J Epidemiol* 2013; **177** (2): 142-151.
38. Trabert B, Troisi R, Grotmol T, Ekblom A, Engeland A, Gissler M, et al. Associations of pregnancy-related factors and birth characteristics with risk of endometrial cancer: a Nordic population-based case-control study. *Int J Cancer* 2020; **146** (6): 1523-1531.
39. Webb PM, Jordan SJ. Epidemiology of epithelial ovarian cancer. *Best Pract Res Clin Obstet Gynaecol* 2017; **41**: 3-14.
40. Wentzensen N, Poole EM, Trabert B, White E, Arslan AA, Patel AV, et al. Ovarian cancer risk factors by histologic subtype: An analysis from the Ovarian Cancer Cohort Consortium. *J Clin Oncol* 2016; **34** (24): 2888-2898.
41. Dick MLB, Siskind V, Purdie DM, Green AC, Australian Cancer Study Group (Ovarian Cancer), Australian Ovarian Cancer Study Group. Incomplete pregnancy and risk of ovarian cancer: results from two Australian case-control studies and systematic review. *Cancer Causes Control* 2009; **20** (9): 1571-1585.
42. Mucci LA, Dickman PW, Lambe M, Adami H-O, Trichopoulos D, Riman T, et al. Gestational age and fetal growth in relation to maternal ovarian cancer risk in a Swedish cohort. *Cancer Epidemiol Biomarkers Prev* 2007; **16** (9): 1828-1832.
43. Jordan SJ, Green AC, Nagle CM, Olsen CM, Whiteman DC, Webb PM, et al. Beyond parity: association of ovarian cancer with length of gestation and offspring characteristics. *Am J Epidemiol* 2009; **170** (5): 607-614.
44. Mogren I, Stenlund H, Högberg U. Long-term impact of reproductive factors on the risk of cervical, endometrial, ovarian and breast cancer. *Acta Oncol* 2001; **40** (7): 849-854.
45. Baik CS, Strauss GM, Speizer FE, Feskanich D. Reproductive factors, hormone use, and risk for lung cancer in postmenopausal women, the Nurses' Health Study. *Cancer Epidemiol Biomarkers Prev* 2010; **19** (10): 2525-2533.
46. Cnattingius S, Eloranta S, Adami HO, Axelsson O, Dickman PW, Hsieh C-c, et al. Placental weight and risk of invasive epithelial ovarian cancer with an early age of onset. *Cancer Epidemiol Biomarkers Prev* 2008; **17** (9): 2344-2349.
47. Sung HK, Ma SH, Choi JY, Hwang Y, Ahn C, Kim B-G, et al. The effect of breastfeeding duration and parity on the risk of epithelial ovarian cancer: a systematic review and meta-analysis. *J Prev Med Public Health* 2016; **49**: 349-366.
48. Sköld C, Björge T, Ekblom A, Engeland A, Gissler M, Grotmol T, et al. Preterm delivery is associated with an increased risk of epithelial ovarian cancer among parous women. *Int J Cancer* 2018; **143** (8): 1858-1867.
49. Sköld C, Björge T, Ekblom A, Engeland A, Gissler M, Grotmol T, et al. Pregnancy-related risk factors for sex cord-stromal tumours and germ cell tumours in parous women: a registry-based study. *Br J Cancer* 2020; **123** (6): 161-166.
50. Sköld C, Koliadi A, Enblad G, Ståhlberg K, Glimelius I. Parity is associated with better prognosis in ovarian germ cell tumors, but not in other ovarian cancer subtypes. *Int J Cancer* 2022; **150** (5): 773-781.
51. Jones MS, Lee J, Stern SL, Faries MB. Is pregnancy-associated melanoma associated with adverse outcomes? *J Am Coll Surg* 2017; **225** (1): 149-158.
52. Caimi S, De Angelis SP, Corso F, Fantini C, Raimondi S, Pala L, et al. Exogenous sex hormones, menstrual and reproductive history, and risk of non-melanoma skin cancer among women: a systematic literature review and meta-analysis. *Sci Rep* 2021; **11** (1): 8524.

53. Costas L, Lujan-Barroso L, Benavente Y, Allen NE, Amiano P, Ardanaz E, et al. Reproductive factors, exogenous hormone use, and risk of B-cell non-Hodgkin lymphoma in a cohort of women from the European Prospective Investigation Into Cancer and Nutrition. *Am J Epidemiol* 2019; **188** (2): 274-281.
54. Tanaka S, Sawada N, Yamaji T, Shimazu T, Goto A, Iwasaki M, et al. Female reproductive factors and risk of lymphoid neoplasm: The Japan Public Health Center-based Prospective Study. *Cancer Sci* 2019; **110** (4): 1442-1452.
55. Lambe M, Hsieh CC, Tsaih SW, Adami J, Glimelius B, Adami HO. Childbearing and the risk of Hodgkin's disease. *Cancer Epidemiol Biomarkers Prev* 1998; **7** (9): 831-834.
56. Weibull CE, Eloranta S, Smedby KE, Björkholm M, Kristinsson SY, Johansson AL, et al. Pregnancy and the risk of relapse in patients diagnosed with Hodgkin lymphoma. *J Clin Oncol* 2016; **34** (4): 337-344.
57. Øvrlisen AK, Jakobsen LH, Eloranta S, Kragholm KH, Hutchings M, Frederiksen H, et al. Parenthood rates and use of assisted reproductive techniques in younger Hodgkin lymphoma survivors: A Danish population-based study. *J Clin Oncol* 2021; **39** (31): 3463-3472.
58. Weibull CE, Johansson ALV, Eloranta S, Smedby KE, Björkholm M, Lambert PC, et al. Contemporarily treated patients with Hodgkin lymphoma have childbearing potential in line with matched comparators. *J Clin Oncol* 2018; **36** (26): 2718-2725.
59. Ekström K, Wu J, Hsieh CC, Glimelius B, Lambe M. Childbearing and the risk of leukemia in Sweden. *Cancer Causes Control* 2002; **13** (1): 47-53.
60. Larfors G, Höglund M, Cnattingius S. Pregnancy and risk of acute myeloid leukaemia – a case-control study. *Eur J Haematol* 2011; **87** (2): 169-171.
61. Burningham Z, Hashibe M, Spector L, Schiffman JD. The epidemiology of sarcoma. *Clin Sarcoma Res* 2012; **2** (1): 14.
62. Fioretti F, Tavani A, Gallus S, Negri E, Franceschi S, La Vecchia C. Menstrual and reproductive factors and risk of soft tissue sarcomas. *Cancer* 2000; **88** (4): 786-789.
63. Kitahara CM, Schneider A, Brenner AV. *Chapter 44: Thyroid Cancer*. 2016.
64. Dal Maso L, Bosetti C, La Vecchia C, Franceschi S. Risk factors for thyroid cancer: an epidemiological review focused on nutritional factors. *Cancer Causes Control* 2009; **20** (1): 75-86.
65. Zamora-Ros R, Rinaldi S, Biessy C, Tjønneland A, Halkjaer J, Fournier A, et al. Reproductive and menstrual factors and risk of differentiated thyroid carcinoma: the EPIC study. *Int J Cancer* 2015; **136** (5): 1218-1227.
66. Horn-Ross PL, Canchola AJ, Ma H, Reynolds P, Bernstein L. Hormonal factors and the risk of papillary thyroid cancer in the California Teachers Study cohort. *Cancer Epidemiol Biomarkers Prev* 2011; **20** (8): 1751-1759.
67. Vandraas KF, Grjibovski AM, Stoer NC, Troisi R, Stephansson O, Ording AG, et al. Hyperemesis gravidarum and maternal cancer risk, a Scandinavian nested case-control study. *Int J Cancer* 2015; **137** (5): 1209-1216.
68. Crump C, Sundquist J, Sieh W, Winkleby MA, Sundquist K. Fetal growth and subsequent maternal risk of thyroid cancer. *Int J Cancer* 2016; **138** (5): 1085-1093.
69. Kabat GC, Kim MY, Wactawski-Wende J, Lane D, Wassertheil-Smoller S, Rohan TE. Menstrual and reproductive factors, exogenous hormone use, and risk of thyroid carcinoma in postmenopausal women. *Cancer Causes Control* 2012; **23** (12): 2031-2040.
70. Guan HB, Wu L, Wu QJ, Zhu J, Gong T. Parity and pancreatic cancer risk: a dose-response meta-analysis of epidemiologic studies. *PLoS One* 2014; **9** (3): e92738.
71. Zhu B, Zou L, Han J, Chen W, Shen N, Zhong R, et al. Parity and pancreatic cancer risk: evidence from a meta-analysis of twenty epidemiologic studies. *Sci Rep* 2014; **4**: 5313.
72. Luo AJ, Feng RH, Wang XW, Wang FZ. Older age at first birth is a risk factor for pancreatic cancer: a meta-analysis. *Hepatobiliary Pancreat Dis Int* 2016; **15** (2): 125-130.
73. Guan HB, Wu QJ, Gong TT. Parity and kidney cancer risk: evidence from epidemiologic studies. *Cancer Epidemiol Biomarkers Prev* 2013; **22** (12): 2345-2353.
74. Gissler M. Routinely collected registers in Finnish health research. Otava, Keuruu: Statistics Finland, 1999.
75. Cappelen I, Daltveit AK, eds. Epidemiological registries – access, possibilities and limitations. *Norsk Epidemiologi* 2004; **14** (1).
76. Coebergh van den Braak RRJ, van Rijssen LB, van Kleef JJ, Vink GR, Berbee M, van Berge Henegouwen MI, et al. Nationwide comprehensive gastro-intestinal cancer cohorts: the 3P initiative. *Acta Oncol* 2018; **57** (2): 195-202.
77. Glimelius B, Melin B, Enblad G, Alafuzoff I, Beskow A, Ahlström H, et al. U-CAN: a prospective longitudinal collection of biomaterials and clinical information from adult cancer patients in Sweden. *Acta Oncol* 2018; **57** (2): 187-194.