

ORIGINAL ARTICLE



Subsequent risk of cancer among women with a history of placental abruption

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ABSTRACT

Background: Placentation is characterized by extensive cell proliferation and neovascularization, which is similar to the processes observed in the development of cancer. Nonetheless, little is known about the relation between abnormal placentation, such as placental abruption, and cancer.

Material and methods: Data on women with placental abruption in a singleton pregnancy between 1971 and 2005 ($n = 7804$) were collected from the Finnish Hospital Discharge Registry and the Finnish Medical Birth Registry. The cohort was then linked with the Finnish Cancer Registry records until the end of 2013. Standardized incidence ratios (SIRs) were calculated for different cancers by dividing the observed numbers of cancers by those expected. The expected numbers were based on national cancer incidence rates.

Results: During follow-up, 597 cancers were found among women with a history of placental abruption. The overall risk of cancer was not increased (SIR 0.95, 95% CI 0.88–1.02). However, the history of placental abruption was associated with an increased risk of lung cancer (SIR 1.51, 95% CI 1.05–2.10) and thyroid cancer (SIR 1.47, 95% CI 1.04–2.02). A decreased risk was found for breast cancer (SIR 0.85, 95% CI 0.75–0.96). The risk of rectal cancer was also decreased, although these numbers were small (SIR 0.49, 95% CI 0.20–1.01).

Conclusions: Overall, the risk of lung cancer was increased, and the risk of breast cancer decreased, in women with a history of placental abruption. These observations can be explained to some extent by risk factors or risk markers for placental abruption. The increased risk of thyroid cancer may be explained by surveillance bias.

Abbreviations: AFP: α -Fetoprotein; CI: confidence interval; HDR: Hospital Discharge Registry; ICD: International Classification of Diseases; MBR: Medical Birth Registry; SIR: standardized incidence ratio

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Introduction

Placental abruption, defined as partial or complete separation of the placenta before delivery, is an obstetric emergency. Placental abruption affects approximately 0.5–1% of deliveries worldwide [1,2]. Although rare, placental abruption causes many risks to the mother and the fetus. The immediate maternal risks are caused by bleeding [3].

Placentation is characterized by extensive cell proliferation and neovascularization, which is similar to the phenomena that occur during cancer development. In placental syndromes, such as placental abruption and preeclampsia, trophoblastic invasion in the spiral arteries and subsequent early vascularization may be defective [4]. Women with placental abruption may have an antiangiogenic imbalance. Angiogenesis is necessary for the growth and spread of solid cancers. Hence, women with placental abruption may have a decreased risk of solid tumors later in life, because antiangiogenesis may also hinder the formation and spread of cancer.

However, only a few studies have assessed the impact of angiogenic factors in the prediction of placental abruption [5,6], and more research is needed.

There is a growing body of evidence linking placental syndromes [7] with long-term maternal morbidity and mortality [8–11]. Preceding studies suggest a reduced risk of subsequent breast cancer among women with a history of preeclampsia [12–15]. However, the link between placental abruption and subsequent cancer has not been well studied. In one study, the risk of breast cancer following placental abruption was nearly double [12]. We previously reported an increased lung-cancer mortality among Finnish women with a history of placental abruption [8].

Multiple risk factors, or risk markers, have been identified for placental abruption [16]. Of these, smoking and alcohol use also expose to cancer. Changes in hormone or protein profile have decreased cancer risk in women with a history of preeclampsia [17]. Some of these changes also act as risk markers for placental abruption [18].

Our aim was to describe the subsequent cancer risk among women with a history of placental abruption, with special emphasis on cancers of the lung and breast.

Material and methods

This was a historical prospective population-based cohort study using linked data from national registries in Finland. The individual was recognized in different registries by using a personal identity code assigned to all Finnish citizens. The data on women with a history of placental abruption were collected from the Hospital Discharge Registry (HDR) and the Medical Birth Registry (MBR), maintained by the National Institute for Health and Welfare. All patients with the diagnosis of placental abruption who delivered between 1971 and 2005 were identified. We used the International Classification of Diseases (ICD) codes ICD-8 codes 632.1, 632.4, and 632.2 for the years 1971–1986; ICD-9 codes 641.20, 641.21, and 641.23 for 1987–1995; and ICD-10 codes O45.0, O45.8, and O45.9 for the years after 1996 in the HDR; and a checkmark on placental abruption (yes/no) in the MBR (October 1990–2005).

The HDR includes data of all inpatient diagnoses from 1971 and also of outpatient diagnoses from public hospitals from 1998. The diagnoses made in primary care or in private outpatient units are not included. In the HDR, the diagnoses are classified according to ICD-8 (1971–1986), ICD-9 (1987–1995), and ICD-10 since 1996. The MBR includes data on interventions the mothers received during pregnancy and delivery. Less than 0.1% of all births are missing from the MBR. The registry data have been validated and correspond well with data available from hospital records [19,20].

The Finnish Cancer Registry includes information on cancers diagnosed in Finland since 1953. Over the decades, more than 99% of cancers have been reported to the Registry [21]. The cancers are classified according to the ICD-O-3 system. The records of women with a diagnosis of placental abruption from the MBR and the HDR were linked with diagnosed cancers from the Finnish Cancer Registry by using their personal identity codes. The follow-up for subsequent cancer started from the date of abruption and ended at death, first emigration, or on 31 December 2013, whichever was first. The dates on emigration and death were collected from the Finnish Population Information System.

The numbers of observed cancers and person-years at risk among women with a history of placental abruption were calculated by 5-year age groups, by calendar periods, and by follow-up periods (<5 months, from 5 months to 5 years, from 5–15 years, and >15 years since the abruption). The numbers of expected cancers were calculated by multiplying the number of person-years in each stratum by the corresponding cancer incidence rate among women in Finland. The standardized incidence ratios (SIRs) were calculated as the ratios of observed to expected numbers of cancers. The 95% confidence intervals (CIs) for the SIRs were based on the presumption that the number of observed cases followed a Poisson distribution.

The permission to utilize and merge registry data for this study was given by the National Institute for Health and Welfare (the registry keeper) (permission number THL/1202/5.05.00/2013, amendment 7 June 2017) as required by national data protection legislation.

The protocol for this study was approved by the Ethical Committee of Helsinki University Hospital (permission number HUS/1736/2017, approved 15 June 2017). As this study used routinely collected anonymized electronic health records, no formal patient consent was required.

Results

In total, 7804 women with a history of placental abruption were included in the study cohort (Table 1). The age distribution at the beginning of follow-up is shown in Table 1. The cohort translated into 192,860 person-years of follow-up and the mean follow-up period was 24.7 years.

During the follow-up, 597 cancer cases were detected in the study cohort. The expected number was 628 giving an SIR for all cancers of 0.95 (95% CI 0.88–1.02) (Table 2). We found an increased risk for cancers of the lung and trachea (SIR 1.51, 95% CI 1.05–2.10), the risk being greatest 5–15 years after the placental abruption (SIR 2.44, 95% CI 0.98–5.03) (Table 3).

The risk for breast cancer was decreased among women with a history of placental abruption (SIR 0.85, 95% CI 0.75–0.96). The risk was reduced for ductal (SIR 0.80, 95% CI

Table 1. Age distribution of the women with placental abruption.

Age	Persons (%)	Person-years (%)
<20	348 (4.5)	423.0 (0.2)
20–29	3922 (50.3)	19,988.7 (10.4)
30–39	3202 (41.0)	59,432.5 (30.8)
>40	332 (4.3)	113,015.9 (58.6)
Total	7804	192,860.1

Age of persons defined in the beginning of follow-up, person-year calculations based on dynamic age.

Table 2. Observed (Obs) and expected (Exp) numbers of cancer cases and standardized incidence ratios (SIR) with 95% confidence intervals (CI) among women with a history of placental abruption during 1971–2013.

Cancer site	Obs	Exp	SIR	95% CI
Any site	597	628	0.95	0.88–1.02
Stomach	8	10.87	0.74	0.32–1.44
Colon	29	24.76	1.17	0.78–1.68
Rectum	7	14.18	0.49	0.20–1.01
Pancreas	9	11.83	0.76	0.35–1.44
Lung, trachea	35	23.15	1.51	1.05–2.10
Melanoma of the skin	18	27.08	0.66	0.39–1.05
Skin, non-melanoma	12	8.20	1.46	0.76–2.55
Soft tissues	6	4.65	1.29	0.47–2.80
Breast	234	273.85	0.85	0.75–0.96
Cervix uteri	17	12.38	1.37	0.80–2.19
Corpus uteri	25	31.80	0.79	0.51–1.16
Ovary	18	25.43	0.71	0.42–1.11
Other female genital	7	5.73	1.22	0.49–2.51
Kidney	15	11.98	1.25	0.70–2.06
Bladder, urinary tract	6	5.94	1.01	0.37–2.19
Brain, central nervous system	36	35.45	1.02	0.71–1.40
Thyroid gland	37	25.14	1.47	1.04–2.02
Leukemia	15	9.14	1.64	0.92–2.70
Hodgkin lymphoma	7	3.52	1.99	0.80–4.09
Non-Hodgkin lymphoma	17	20.91	0.81	0.47–1.30

Table 3. Selected cancer diagnoses and standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) among women with a history of placental abruption by duration of follow-up.

Cancer site	Years since placental abruption								
	<5			5–14.99			15+		
	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)
Lung, trachea	–	0.49	0.00 (0.00–7.55)	7	2.86	2.44 (0.98–5.03)	28	19.80	1.51 (1.05–2.10)
Breast	9	11.23	0.80 (0.37–1.52)	54	62.07	0.87 (0.65–1.13)	171	200.56	0.85 (0.75–0.96)
Thyroid	6	3.22	1.86 (0.68–4.05)	14	8.76	1.60 (0.87–2.68)	17	13.16	1.29 (0.75–2.06)
Rectosigmoid	–	0.43	0.00 (0.00–8.54)	1	2.42	0.41 (0.01–2.30)	6	11.33	0.53 (0.19–1.15)

0.69–0.93), but not for lobular (SIR1.07, 95% CI 0.78–1.42) cancers of the breast (data not shown). No difference was seen between pre- and post-menopausal ages.

We observed an increased risk for thyroid cancer (SIR 1.47, 95% CI 1.04–2.02). The vast majority of the cases (35 out of 37 cases) consisted of the papillary subtype of thyroid cancer (SIR 1.62, 95% CI 1.13–2.25).

The risk of rectal cancer was reduced although the decrease was not statistically significant because of small numbers (SIR 0.49, 95% CI 0.20–1.01).

The incidence of other cancers did not differ from that in the reference population.

Discussion

Our principal findings were that the risk for lung cancer and thyroid cancer was increased while the risk for breast cancer was decreased among women with a history of placental abruption.

The association between lung cancer and a history of placental abruption was not unexpected, since smoking is one of the most important risk factors both for placental abruption [2,3,22–24] and for lung cancer [25]. We previously reported that women with a history of placental abruption had increased mortality of respiratory tract cancers [8]. The underlying mechanisms of the association between smoking and placental abruption are most likely related to underperfusion of the uterus. This may lead to lesions (i.e., decidual necrosis, placental microinfarcts, fibroid changes, and atrophic placental villi) that are consistent with chronic hypoxic changes in the placenta. Increased fragility might result in arterial rupture leading ultimately to placental abruption [26]. Although there is an increased risk for lung cancer among women with a history of placental abruption the underlying mechanism for this is unknown. The most probable explanation is heavy smoking although this has not been proven. We were not able to compare the smoking habits of our study cohort to general female population, but previous studies have shown that women with placental abruption smoke more often and more heavily than reference women during pregnancy [26]. There are no studies showing whether the placental abruption has an effect on continuation of smoking.

The link between placental abruption and subsequent cancer incidence has not been extensively studied. A US case-control study [12] reported an association between breast cancer and placental abruption (OR 1.8, 95% CI 1.1–3.0). Cases were defined as breast cancer patients who

had had their first delivery at least 1 year before the cancer diagnosis. The result of this study is contradictory to our finding of a reduced breast cancer risk among women with a history of placental abruption. However, the study design was different. Thus, these two reports cannot be considered directly comparable. Cancer risk among women with preeclampsia has been studied more extensively. In most of the studies the risk of breast cancer has been decreased [12–15] and might be due to different hormone or protein profile. For instance, high gestational levels of α -fetoprotein (AFP) may protect against subsequent development of breast cancer [27]. On the other hand, high gestational levels of AFP are also associated with increased risk of placental abruption [18,28,29]. Thus, elevated maternal serum AFP could, to some extent, explain the decreased risk of subsequent breast cancer in women with a previous abruption. Preeclampsia is also a risk factor for placental abruption [16]. Since these two conditions share similar histopathologic features [30], our finding of a reduced risk of breast cancer among women with a history of placental abruption seems biologically plausible.

Parity is another feature that should be considered when discussing cancer risks among women with a history of abruption. It is known from a study of the Finnish Maternity Cohort that the incidence of breast cancer in women with at least three children is about one-tenth below the rate of all Finnish women [31]. For breast, endometrial and ovarian cancer, each pregnancy provides an additional long-term risk reduction. In breast cancer, the risk increases transiently after childbirth but reduces in later years [32]. Multiparity (three or more previous deliveries) increases the risk for placental abruption [18]. This may partly explain the decreased breast cancer risk among women with a history of abruption.

We observed an increased risk of papillary thyroid cancer among women with a history of abruption. This observation may be due to surveillance bias. Hypothyroidism is a risk factor for placental abruption [33,34]. Hence, in cases of abruption, the women may undergo evaluation of the thyroid gland which in turn may result in detection bias. Finally, there were only seven cases of rectal cancer among women with a history of placental abruption, while the expected number was 14. This finding may be considered a chance finding.

Some strengths and limitations of our study warrant attention. The study cohort was large, comprising more than 7800 women with a history of placental abruption, and average follow-up was almost 25 years. The completeness and quality of the Finnish population-based registers further improves the credibility of our results [21,35,36]. However,

the cohort is quite young and the actual number of detected cancers is still relatively small. This limits the conclusions that may be drawn. Furthermore, data were unavailable regarding smoking and other factors, such as parity, which might have an effect on future cancer risk. Smoking is a strong risk factor for both placental abruption and lung cancer. Thus, the observed association between placental abruption and lung cancer may not be a true causal association but rather due to confounding by smoking. Therefore, this result should be interpreted with caution.

To the best of our knowledge, this is the first study of the overall cancer risk among women with a history of placental abruption. We observed increased risks for lung cancer and thyroid cancer and a reduced risk for breast cancer. The risk for other malignancies, as well as the overall cancer risk among women with a history of abruption were similar to that in the general Finnish female population. It is unlikely that placental abruption as such has an effect on increased cancer risk.

Disclosure statement

No potential conflict of interest was reported by the authors.

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