



## Intrahepatic Cholestasis of Pregnancy and Cancer: A Cohort Study

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### Abstract

**Objective:** In a previous questionnaire study, more breast cancers were reported by women with intrahepatic cholestasis of pregnancy (ICP) than by the controls. The aim of this study was to establish whether ICP is associated with cancer in the Finnish Cancer Registry data, the study population being the same cohort as in the questionnaire study.

**Methods:** The study population comprised 571 women with ICP in at least one pregnancy and 1,333 controls from Tampere University Hospital in Finland during 1969–1988. The cancer data were obtained from the Finnish Cancer Registry. The cancers were classified by ICD-O-3 and diagnosed during the period 1953–2013.

**Results:** In the ICP group, the odds ratio of cancers (OR 1.26, 95% CI 0.96–1.64), and breast cancer in particular (OR 1.36, 95% CI 0.91–2.03), was slightly higher than in the control group. Seven percent of the ICP group and 5.3% of the control group had breast cancer.

**Conclusion:** Based on this study there is not a significant association between ICP and cancer. Earlier observation in the questionnaire study regarding association between ICP and breast cancer cannot be confirmed by this registry based study.

**Keywords** Intrahepatic cholestasis of pregnancy; ICP; Cancer

### Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a reversible liver disorder with pruritus as the main symptom, especially on the palms and soles. An elevated serum bile acid and transaminase concentration is also required for diagnosis [1]. In Europe, the incidence of ICP is approximately 1%, but rates vary geographically [2]. In Finland, the incidence is approximately 1.0–1.5% [3] and in Sweden the incidence is 0.5–0.75% [4]. Hormonal factors seem to contribute to the pathogenesis of ICP [5,6]. Estrogen may participate in the development of cholestasis [7] and progesterone may impair hepatic bile homeostasis [8]. Genetic factors are known to be involved in the pathogenesis; ICP is inherited as a sex-limited dominant phenotype and multiple genes are influential [9]. Multidrugresistant protein 3 (MDR3) is associated with up to 15% of ICP cases [10,11]. Environmental factors may also have a role in the pathogenesis of the disorder [12]. In addition, a positive family history [13] and twin pregnancies raise the risk of ICP [14].

Excessive exposure of endogenous estrogen over the lifetime may be a causative factor of breast cancer [15]. Hormonal, genetic, and environmental factors are known to have an impact on the aetiology and pathogenesis of cancers and ICP. Cancer antigen 15-3 (CA15-3) is a glycoprotein commonly found in breast cancer cells, and its levels in serum reflect the amount of breast cancer cells in the body. CA15-3 levels are raised during pregnancy in general, but they are higher in

ICP pregnancies than in controls [16]. In an extensive registry-based study, ICP was associated with an increased risk for later hepatobiliary cancer. Hepatitis C infection was strongly associated with liver cancer, but after adjusting for this diagnosis, women with ICP were still at increased risk for liver malignancy. In addition, in a separate analysis excluding all women with gallstone disease or cholangitis, women with ICP had an increased risk for biliary tree malignancies [17].

A low number of child births has been associated with an increased risk for breast cancer. Since mothers with ICP have been found to limit their child number more often than controls [18], it may be speculated whether this has increased the incidence of breast cancers. Primary healthcare arranges almost exclusively maternity care in the Nordic countries [19]. In Finland health centres maintain maternity health clinics where a nurse or a midwife and a Family Doctor are responsible for care [20]. The maternity health clinics in primary health care usually detect ICP. If a pregnant woman complains of pruritus her ALAT and bile acids values are screened. Either of these values being elevated the mother is referred to an obstetrician [21]. If pruritus is intolerable the mother is referred to the obstetric clinic without waiting the results of the blood test.

A questionnaire study observed that ICP may be associated with an elevated risk for breast cancer [22]. However, the study was based on subjective information obtained from self-reports. The aim of the present study was to investigate, using objective registry data, whether ICP has an association with breast cancer or other cancers when using the same cohort as the questionnaire study.

## Material and Methods

All ICP pregnancies at Tampere University Hospital (TUH) during 1969–1988 were collected from the patient records. From 1969 to 1986, ICD-8 was used at TUH. Because ICD-8 did not include a precise code for ICP, we checked all the obstetric codes that might contain ICP: 637.9 Toxicosis NUD, 639.00 Pruritus, 639.01 Icterus gravis, 639.09 Necrosis acuta et subacuta hepatitis, and 639.98 Aliae definitae. Thereafter, we checked the written diagnosis behind the code, and if it referred to ICP, we included the case for further selection. ICD-9 was used between 1987 and 1988, and it contained the appropriate codes 6467A Hepatosis gravidarum and 6467X Hepatopathia alia. The diagnosis was verified from each patient record with the presence of the main symptom of itching and abnormal laboratory test results. At least one of the following was required: ASAT >35 U/l, ALAT >40 U/l, or bile acids 6 µmol/l or more.

The study population comprised 687 ICP deliveries. The data included some women with repeated ICP deliveries and each of these women was studied as an individual case. The ICP group thus contained 575 women. The proceeding and following subjects in the maternity ward diary were taken as controls for each ICP case. There were 1,374 controls in total. The groups were comparable regarding age, educational level, and body mass index. The deliveries of mothers with ICP took place at earlier gestational weeks than those of the controls. Four women were ruled out from the ICP cases and 41 from the controls because of a missing personal identity code. The final data comprised 571 women with ICP and 1,333 controls.

The cancer data were obtained from the Finnish Cancer Registry in January 2014 based on personal identity codes. All physicians, hospitals, and other relevant institutions have had an obligation to report every cancer to the Finnish Cancer Registry since 1961. The database contains all the diagnosed cancers and cancer deaths in Finland since 1961 and the most of cancers since 1953, when systematic cancer registration was started [23]. The Finnish Cancer Registry also contains information on all death certificates that mention cancer. The Registry takes notice of the completeness and accuracy of its data, and its completeness has been shown to be over 99% [24]. The Registry is upheld by the National Institute for Health and Welfare of Finland. The study data included all reported cancers of the cohort during 1953–1960, all registered cancers during 1961–2013, and the location and behaviour of the cancer. The cancers were reported by ICD-O-3 topographical codes [25]. Women who had had more than one cancer were also included in the study. The cancers were classified by ICD-O-3 codes into larger subgroups. Cancer behaviour was classified as benign, unclear behaviour, carcinoma in situ, or malignant.

The data were analysed using the SPSS System for Windows, Version 22.0. The results are presented as frequencies and percentages. Statistical significance was tested with a chi-squared test. Binary logistic regression analysis was performed to obtain odds ratios (OR) and 95% confidence intervals (CI). The dependent variable was “ICP or not”. T-test was performed to explore difference regarding age at the diagnose moment of cancer. The cohort did not obtain informed consent because the study is retrospective and does not have an effect on treatment. The study has the approval of the Regional Ethics Committee of Tampere University Hospital (R02149) and the National Institute for Health and Welfare in Finland (THL/1051/5.05.00/2014).

## Results

In the ICP group, 96 women (16.8%) had been diagnosed with at least one cancer, compared to 185 women (13.9%) in the control group. The difference was not statistically significant ( $p=0.098$ ). Mothers with ICP had a slightly higher risk for cancer (OR 1.26, 95% CI 0.96–1.64) than the control mothers. None of the mothers with ICP and fifteen (1.1%) of the controls had been diagnosed with two or more separate cancers ( $p=0.011$ ). One of the controls had had three separate cancers. Three women had been diagnosed with a cancer before labour and all of them were controls.

The occurrence of cancers is presented in Table 1. Breast cancer was the most common cancer in both groups. The mothers with ICP had a slightly higher risk for breast cancer (OR 1.36, 95% CI 0.91–2.03) than the control mothers. Breast cancer was diagnosed at a slightly older age in the ICP group than in the control group but the difference was not statistically significant.

ICD-10 code	Cancer	Mothers with ICP n=571		Control mothers n=1,333		Difference	
		n	%	n	%	% units	p-value
C50	Breast	40	7.0	70	5.3	1.7	0.133
C73-C75	Thyroid and other endocrine glands	6	1.1	5	0.4	0.7	0.075
C64-C68	Urinary tract	4	0.7	3	0.2	0.5	0.116
C42	Haematopoietic and reticuloendothelial systems	2	0.4	2	0.2	0.2	0.382
C30-C39	Respiratory and intrathoracic organs	1	0.2	3	0.2	0.0	0.827
C40-C41	Bone and articular cartilage	1	0.2	3	0.2	0.0	0.827
C80	Unknown primary site	1	0.1	1	0.1	0.0	–
C00-C14	Lip, oral cavity, and pharynx	0	0.0	1	0.1	-0.1	0.513
C15-C26	Digestive organs	7	1.2	19	1.4	-0.1	0.731
C45-C49	Mesothelial and soft tissue	0	0.0	1	0.1	-0.1	0.513
C43-C44	Melanoma and other malignant neoplasms of skin	18	3.2	38	2.9	-0.1	0.721
C51-C58	Female genital organs	14	2.5	35	2.6	-0.1	0.826
C69-C72	Eye, brain, and other parts of central nervous system	3	0.5	8	0.6	-0.1	0.844
C77	Lymph nodes	2	0.4	7	0.5	-0.1	0.610

**Table 1:** The occurrence of cancers in mothers with ICP and the controls.

Melanoma and other malignant neoplasms of the skin as well as cancers of the female genital organs were among the most common cancers in both groups. Cancers of the thyroid and other endocrine glands and urinary tract cancer were more common in the mothers with ICP than in the controls, but the differences were not statistically

significant. Of the digestive organ cancers, hepatobiliary cancer was also examined separately. Hepatobiliary cancer was found in one mother with ICP and among none of controls. Most of the cancers (nearly 90%) were malignant in both groups (Table 2). The difference between the groups was not statistically significant ( $p=0.758$ ).

Cancer behaviour	Mothers with ICP (n=96) (%)	Control mothers (n=185) (%)
Malignant	87.5	86.5
Carcinoma in situ	6.3	5.4
Unclear behaviour	0.0	1.1
Benign	6.3	7.0

**Table 2:** Cancer behaviour according to ICD-O-3 among mothers with ICP and the controls.

The mothers with ICP had been diagnosed with cancer at a slightly older age, the mean age being 53.0 years in the ICP group and 51.8 years in the control group. The difference was 1.2 years ( $p=0.315$ ). The mean age of mothers who had not been diagnosed with cancer was 61.5 years among ICP mothers and 61.3 years among controls in 31/12/2013.

## Discussion

The ICP group and the control group evinced minor differences in most of the study outcome measures. The findings are in agreement with former observations on the association of cancer and ICP. In the control group, there were women who had been diagnosed with two or more separate cancers, but in the ICP group each woman with cancer had been diagnosed with only one cancer. ICP was associated with a slightly higher risk for cancer, especially breast cancer.

The aim of the present study was to establish whether ICP is associated with an increased risk for cancers, and especially for breast cancer, which was the result found from the earlier study based on self-reports. Despite the small loss of cases, the data were adequate. The data obtained from the Finnish Cancer Registry can be considered reliable.

Medications may have an impact on the risk for cancer. Over the past decades, various treatments have been used for ICP. We have not collected information about the medication for ICP among our study population, and consequently the role of medication regarding the risk for cancer cannot be evaluated.

A recent Swedish study did not find any clear association between overall cancer and ICP [17], which is in agreement with our findings. In the same study, an increased risk for later hepatobiliary cancer in women with ICP was found (liver cancer: HR 3.61; and biliary tree cancer: HR 2.62). In the aforementioned study, the occurrence of hepatobiliary cancers was small in the ICP group (0.1–0.2%). Based on the above study, the expectation value to find any hepatobiliary cancers in our study was very small. However, one hepatobiliary cancer was found in our ICP group, which exceeds the expectation value.

There is higher risk of hepatobiliary disease and particularly chronic hepatitis among women with a history of ICP [26,27]. The latter disease causes liver cirrhosis and is often complicated by hepatocellular cancer [17]. Also cholelithiasis and chronic cholangitis are associated with ICP [26,27] and are associated with gallbladder and cholangiocellular cancer [17].

The Swedish registry study did not find any association between breast cancer and ICP (HR 1.03). In our study, mothers with ICP had a slightly higher risk for breast cancer than the control mothers (OR 1.36), although the difference was not statistically significant. The occurrence of breast cancer was lower in the Swedish population (1.6%) than in our Finnish population. Women's risk for having breast cancer before the age of 75 is 9.9% in Finland and 9.6% in Sweden [28]. Our longer follow-up time and the younger age of mothers in the Swedish study might explain the difference. Nevertheless, the cohort should be followed even longer because now the cohort represents those who had been diagnosed with cancer at a fairly young age.

Premature delivery (gestation weeks <37) seems to increase the mother's risk for breast cancer later in life [29]. Formerly, it has been found that ICP is associated with an elevated risk for delivery in gestation weeks under 37 [14]. It can be considered that premature delivery may increase the number of breast cancer cases among ICP women.

A questionnaire study observed that the women with ICP reported more breast cancer (6.3% vs. 3.7%,  $p=0.047$ ) [22]. In our study, breast cancer was found among 7.0% in the ICP group and among 5.3% in the control group, the cohort being the same as in the questionnaire study. In this registry study, however, the difference between the groups is not statistically significant.

ICP has found to have a multifactorial genetic base. It may be speculated that ICP is one expression of a larger group of genetic diseases. Hormonal factors may be relevant in the pathogenesis of ICP and breast cancer [5,6,15]. It may be speculated whether the same hormonal factors have an effect on both diseases.

This is the first Finnish registry study on the potential association between ICP and cancer. According to the writers' knowledge there is only one registry based study investigating the association between ICP and cancer [17], and therefore the findings in this study may be considered unique. However, former observations regarding the association between ICP and breast cancer in the questionnaire study could not be confirmed by this registry based study. A larger number of ICP women and a longer follow-up time of the cohort might be needed to confirm the results. Based on this study doctors do not have to change their treating strategies and screen cancers because a woman has a history of ICP.

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## Conflict of Interest

The authors have no conflicts of interest.

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