

Cancer after pre-eclampsia: follow up of the Jerusalem perinatal study cohort

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Abstract

Objective To compare the incidence of cancer among women with and without a history of pre-eclampsia.

Design Cohort study.

Setting Jerusalem perinatal study of women who delivered in three large hospitals in West Jerusalem during 1964-76.

Participants 37 033 women.

Main outcome measures Age adjusted and multivariable adjusted hazard ratios for cancer incidence for the entire cohort and for women who were primiparous at study entry.

Results Cancer developed in 91 women who had pre-eclampsia and 2204 who did not (hazard ratio 1.27, 95% confidence interval 1.03 to 1.57). The risk of site specific cancers was increased, particularly of the stomach, ovary epithelium, breast, and lung or larynx. The incidence of cancer of the stomach, breast, ovary, kidney, and lung or larynx was increased in primiparous women at study entry who had a history of pre-eclampsia.

Conclusions A history of pre-eclampsia is associated with increases in overall risk of cancer and incidence at several sites. This may be explained by environmental and genetic factors common to the development of pre-eclampsia and cancer in this population.

Introduction

Previous cohort and case-control studies have shown an inconsistent association between risk of cancer and risk of death from cancer in women who have or have not had pre-eclampsia (see bmj.com). Several studies have found that maternal pre-eclampsia reduces the risk of breast cancer up to fourfold in female offspring.¹ We investigated overall cancer incidence as well as incidence at specific sites in women in the Jerusalem perinatal study cohort who had or had not had pre-eclampsia.

Methods

The Jerusalem perinatal study cohort comprises all births in 1964-76 to residents of West Jerusalem. It was intended as a survey of pre-eclampsia, defined as a systolic blood pressure of ≥ 140 mm Hg or a diastolic blood pressure of ≥ 90 mm Hg, or both, together with a proteinuria and oedema. (The current definition excludes oedema²). Baseline data were recorded at birth.³ In 2000 we traced 40 455 (91.8%) of the 44 067 mothers through the Israel population registry using the unique identity number assigned to all Israeli residents. We obtained information on vital status for 39 809 (98.4%) of the traced mothers. Mothers were linked by way of their identity number to the Israel Cancer Registry, which was set up in 1961 and is 94.2%

complete for breast cancer and 95.8% complete for ovarian cancer.⁴

Statistical methods

We used bivariate and multivariate Cox proportional hazards models to assess the risk of cancers at all sites and at specific sites in women with pre-eclampsia recorded at any birth in the cohort (1964-76) and those without pre-eclampsia. We adjusted for age and for other factors associated with pre-eclampsia and cancers at specific sites. Age at entry to the cohort was introduced into the models as a continuous variable. When assessing risk of breast cancer for all mothers, we adjusted for parity and age simultaneously. Other variables tested were social class (by husband's occupation), years of education, ethnic origin, immigration, religion, insulin dependent diabetes mellitus, gestational diabetes, birth weight, and birth defects of the offspring. Follow up was from the first observed birth in the cohort to diagnosis of cancer, death, or 30 June 1999. The analysis was restricted to the 92% of women delivering in the three largest hospitals in West Jerusalem where pre-eclampsia was systematically ascertained. A priori we also studied the subgroup observed from their first birth. For cancers at specific sites, we restricted the analyses to the 17 sites with at least 25 cases.

Results

The analysis included 37 033 women. Pre-eclampsia was recorded in 1070 (2.9%). Pre-eclamptic women were older at baseline (see bmj.com for characteristics of all women in cohort). Entry to the study cohort was at the first completed pregnancy for 57.8% for women with and 61.5% of women without pre-eclampsia. Ethnicity of west Asian origin was more common among women with pre-eclampsia (31.4%) than those without (28.6%). Women with pre-eclampsia were more likely to be of lower social class than those without. Fifty six (5.2%) women with pre-eclampsia had gestational diabetes compared with 349 (1.0%) women without. The median length of follow up was 29 years.

In total, 2295 first primary cancers were reported. After pre-eclampsia there was an overall excess of cancer when all sites were combined (age adjusted hazard ratio 1.27, 95% confidence interval 1.03 to 1.57). The risk of breast cancer was significantly increased for pre-eclamptic women after adjusting for age and parity (1.38, 1.0 to 1.89). The risk of cancers of the stomach, ovary epithelium, and lung or larynx were statistically significantly increased after adjustment for age (table). Multivariable adjustment did not substantially change the hazard ratios.

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Incidence of invasive cancers by site and pre-eclampsia status (sites with at least 25 cases)

Cancer site	No of cases		Age adjusted hazard ratio (95% CI)	P value
	No pre-eclampsia (n=35 963)	After pre-eclampsia (n=1070)		
Stomach	46	5	3.10 (1.23 to 7.84)	0.017
Colon	140	7	1.46 (0.68 to 3.12)	0.333
Rectum	68	2	0.86 (0.21 to 3.53)	0.839
Pancreas	27	2	2.06 (0.49 to 8.70)	0.326
Lung or larynx	53	5	2.81 (1.12 to 7.05)	0.028
Melanoma	126	5	1.28 (0.52 to 3.14)	0.584
Breast*	938	40	1.38 (1.0 to 1.89)	0.046
Cervix	62	0	—	—
Endometrium	70	1	0.44 (0.06 to 3.18)	0.417
Ovary epithelium	79	6	2.32 (1.01 to 5.34)	0.047
Bladder	24	1	1.20 (0.16 to 8.93)	0.856
Kidney	36	2	1.52 (0.36 to 6.32)	0.568
Brain or nervous system	30	1	0.94 (0.12 to 6.94)	0.954
Thyroid	114	3	0.87 (0.28 to 2.75)	0.818
Hodgkin's disease	24	1	1.41 (0.19 to 10.43)	0.736
Non-Hodgkin's lymphoma	90	3	1.08 (0.34 to 3.41)	0.898
Leukaemias	32	0	—	—
All others	245	7	0.86 (0.40 to 1.82)	0.689
Total	2204	91	1.27 (1.03 to 1.57)	0.024

*Adjusted for age and parity.

In the 22 716 women followed from their first birth there was an increased risk after adjustment for age of all cancers (1.58, 1.20 to 2.07) and cancers of the stomach (6.45, 2.16 to 19.3), breast (1.75, 1.19 to 2.58), ovary (3.25, 1.15 to 9.19), kidney (4.83, 1.07 to 21.9), and lung or larynx (2.87, 0.67 to 12.3).

We compared the personal characteristics and outcome of cancer in 2766 women who were excluded from the analysis because they did not deliver in the study hospitals. These women were older at their first birth (mean age 27.3 years for excluded women versus 26.2 for included women) and were more likely to be non-Jewish (6.3% *v* 1.0%) or of European origin (47.2% *v* 34.7%). Cancer occurred in 194 (7.1%), of which 88 (45%) had breast cancer compared with 42.6% in the included cohort.

Discussion

The overall incidence of cancer and site specific cancers of the stomach, ovary, and breast are increased after pre-eclampsia. This was especially noticeable in women followed from their first pregnancy. Results for ovarian and breast cancer were not explained by parity, diabetes, ethnic origin, or social variables. Previous studies on pre-eclampsia have been carried out mainly in northern European or North American populations, as have the studies reporting a protective effect on the risk of breast cancer.⁴⁻⁹

The longer follow up in our study may have brought to light associations not previously observed.⁶⁻⁸ Furthermore, our analysis was restricted to those with and without criteria for pre-eclampsia and did not include all hypertensive diseases of pregnancy, which were coded separately in the database of the Jerusalem perinatal study. This contrasts with other studies.⁵⁻⁷ We minimised the possibility of biases in selection and ascertainment by relying on a population based cohort with near complete follow up. The possibility of differential reporting of cancer or

What is already known on this topic

Some studies have suggested a protective effect of pre-eclampsia on risk of cancer

Few population based studies have been performed

Most have been conducted among northern European or North American populations

What this study adds

Women with a history of pre-eclampsia are at increased risk of cancer, particularly cancers of the stomach, breast, ovary, and lung and larynx

Specific environmental and genetic factors may contribute to the development of both pre-eclampsia and cancer in middle eastern populations

pre-eclampsia status or ascertainment of cancer to the Israel cancer registry is unlikely. Recall bias cannot have played a part.

We adjusted for age and major risk factors for breast and ovarian cancers; however, we cannot rule out residual confounding. It may be difficult to extrapolate our findings to contemporary women since the definition of pre-eclampsia no longer includes oedema. Other limitations are the lack of data on the cohort before 1964 and after 1976. The possibility remains that some results may be chance findings, as the number of cancers at specific sites is small.

Ashkenazic (European Jewish) populations are at increased risk of particular cancers, such as breast and ovarian cancers, due to mutations in particular genes involved in DNA repair; but only a third of our cohort originated in Europe.²⁻¹⁰ Furthermore, such genes are not known to contribute to pre-eclampsia. Other mutations in genes affecting thrombophilia or hyperhomocysteinaemia or those influencing angiogenesis and trophoblast invasion might be associated with pre-eclampsia and cancer in our population.¹¹⁻¹² We did not adjust for smoking history because of insufficient data. Nevertheless the finding of increased lung or larynx cancer among those with previous pre-eclampsia is intriguing given the purported protective effect of smoking in pre-eclampsia.¹³ On the other hand polymorphisms in the human epoxide hydrolase (a detoxifying enzyme) gene have been associated with both lung and larynx cancer as well as pre-eclampsia, providing a possible mechanism for this association.¹⁴⁻¹⁶ Evidence is emerging for differential effects of candidate genes in the pathogenesis of pre-eclampsia among different populations.¹⁷ Alternatively, diet (for example, folate intake), insulin resistance, smoking, or patterns of infection might represent common pathways in the pathogenesis of cancer and pre-eclampsia, and their effects might be expected to differ between populations.

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Incidence of breast cancer in Norway and Sweden during introduction of nationwide screening: prospective cohort study

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Abstract

Objective To determine whether any increase in the incidence of breast cancer in women detected by mammography is compensated for by a drop in the incidence after age 69, years when women are no longer invited for screening.

Design Population based cohort study of incidence of breast cancer during the introduction of nationwide screening programmes.

Setting Norway and Sweden.

Participants All women aged above 30 years (1.4 and 2.9 million, respectively, in 2000).

Main outcome measures Changes in age specific incidence rates of invasive breast cancer associated with the introduction of the screening programmes.

Results As a result of screening the recorded incidence of breast cancer in women aged 50-69 years increased by 54% in Norway and 45% in Sweden. There was no corresponding decline in incidence after the age of 69 years.

Conclusions Without screening one third of all invasive breast cancers in the age group 50-69 years would not have been detected in the patients' lifetime. This level of overdiagnosis is larger than previously reported.

Introduction

Overdiagnosis in cancer screening is defined as the detection of low malignancy lesions that otherwise would not be detected in a patient's lifetime. It is often argued that overdiagnosis is not a problem for screening in breast cancer.¹⁻³ For example, Boer et al

predicted a 31% increase in incidence of breast cancer in the Dutch mass screening programme that would be nearly fully compensated for by a strong drop in the incidence after age 69 years, when women are no longer invited for screening.¹ Altogether there should be only 2% more breast cancers.¹

Olsen and Gøtzsche reported 30% overdiagnosis in various screening trials.⁴ In Finland, incidence rates of breast cancer associated with screening have also increased.⁵ In Australia Harmer et al suggested that a recent increase in incidence is entirely due to mammographic screening.⁶

Organised nationwide screening for breast cancer with mammography in the age group 50-69 years started in Sweden in 1986⁷ and in Norway in 1996.⁸ We studied the increase in age specific incidence rates for invasive breast cancer for the period 1971-2001 in Norway and Sweden.

Methods

In 1996-7 around 165 000 women in four counties (Akershus, Oslo, Rogaland, Hordaland—the AORH counties) in Norway, covering 40% of the population, were invited to mammographic screening for the first time. They attended for second screening in 1998-9 and third in 2000-1. Screening in the 15 other counties started gradually later. In Sweden screening was introduced from 1986 to 1996. More than 90% of the million women in the age group 50-69 years had been

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