Innate left handedness and risk of breast cancer: case-cohort study

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Among the proposed origins of breast cancer are intrauterine influences, such as exposure to sex hormones.[1] Such exposure may also influence cerebral lateralisation, with hand preference being one of its manifestations. We know only of case-control studies on a putative common origin of left handedness and breast cancer, some of which show an association.[2] We assessed the association between handedness and incidence of breast cancer in a population based prospective cohort of healthy, middle aged women followed up for 16 years.

Participants, methods, and results

In a breast cancer screening study in Utrecht, the Netherlands, 12 178 women born between 1932 and 1941 and recruited between 1982 and 1985 (participation rate 40%) had baseline questionnaire data recorded about reproductive history, demography, lifestyle, and innate hand preference and had anthropometric measures taken. Linkage with the regional cancer registry provided data on all new cases of invasive breast cancer that occurred until 1 January 2000. Follow-up for adequate information about the person years lived for all 12 178 women would have been costly and time consuming, so we ascertained vital status until 1 January 2000 in a random selection of 1500 women and used their follow-up data to calculate person years lived in the 12 178 women. Exclusion of women with incomplete data left 1426 women; 55 women from the random sample and 371 from outside the random sample had breast cancer (incidence of breast cancer 2.5 per 1000 person years). We used Prentice's method for Cox regression as recommended by Barlow and colleagues[3] for analysis with the statistical software SAS (version 8.2, SAS Institute, NC, USA) and a dedicated macro (http://lib.stat.cmu.edu/general/robphreg).

The random sample comprised 165 (11.6%) left handed women. Mean age at baseline was similar for left and non-left handed women (47.4 (range 41.6-53.1) and 47.0 (41.0-53.1) years respectively). These groups did not differ in anthropometry, socioeconomic status, smoking habits, family history of breast cancer, or reproductive history (except for parity—21.8% of left handed *v* 10.9% of non-left handed women were nulliparous).

The relative risk for breast cancer in left handed women compared with non-left handed women was

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Association between handedness and incidence of breast cancer in study participants followed up at 16 years

Innate handedness	Cases	Estimated person years*	Hazard ratio (95% confidence interval)	
			Crude	Adjusted†
Total				
Non-left handed	361	153 422	1.00	1.00
Left handed	65	19 119	1.39 (1.09 to 1.81)	1.32 (0.99 to 1.76)
Premenopausal breast cancer				
Non-left handed	57	32 113	1.00	1.00
Left handed	15	3329	2.41 (1.35 to 4.30)	2.20 (1.15 to 4.20)
Postmenopausal breast cancer				
Non-left handed	257	127 426	1.00	1.00
Left handed	39	17 665	1.12 (0.80 to 1.57)	1.05 (0.75 to 1.48)
Body mass index ≤25				
Non-left handed	217	95 964	1.00	1.00
Left handed	45	11 332	1.62 (1.17 to 2.24)	1.59 (1.15 to 2.20)
Body mass index >25				
Non-left handed	144	57 458	1.00	1.00
Left handed	20	7787	1.05 (0.67 to 1.66)	1.04 (0.65 to 1.64)
Nulliparous				
Non-left handed	61	16 486	1.00	1.00
Left handed	9	3759	0.68 (0.35 to 1.32)	0.70 (0.36 to 1.35)
Parous				
Non-left handed	300	136 936	1.00	1.00
Left handed	56	15 360	1.58 (1.19 to 2.11)	1.59 (1.18 to 2.13)

The non-left handed group was the reference group.
74 random sample participants and 32 cases with missing data on covariates or prevalent cases were excluded from these analyses.
Fifty eight breast cancer cases were not analysed as premenopausal or postmenopausal breast cancer because menopausal information was not available and the age at diagnosis was 51-55 years.
*The number of person years (lived in the total cohort) is extrapolated from the random sample.
†Adjusted for socioeconomic status, age, height, body mass index (except in body mass index specific analysis), smoking status, history of breast cancer in mother or sister, age at menarche, parity status (except in parity specific analysis), all at baseline; adjusted for age at last known menstruation and menopausal status during follow-up (except for outcome of premenopausal or postmenopausal breast cancer).

1.39 overall (table). The risk was 2.41 when the cancer was premenopausal (diagnosis before reported onset of menopause or, if menopausal data were unavailable, diagnosis at age <51 years), but there was no excess risk for postmenopausal cancers (table)). Adjustment for risk factors hardly affected the overall association between left handedness and incidence of breast cancer. We found an excess risk for breast cancer in left handed women with a body mass index of ≤25 but not in those whose index was >25 (P interaction 0.07), and in parous but not nulliparous women (P interaction 0.02).

Comment

We found that left handed women are more than twice as likely to develop premenopausal breast cancer as non-left handed women. This risk is compatible with left handedness being a marker of constitutional risk rather than of environmental risk as with postmenopausal breast cancer.

Our findings among premenopausal women may be compatible with a stronger association in women with a normal body mass index, as high body mass index is a particular risk factor for postmenopausal breast cancer. However, our data did not allow for a robust analysis of this issue.

The origin of the association may lie in intrauterine exposure to steroid hormones, as supported by data showing a higher prevalence of left handedness in women with intrauterine exposure to diethylstilbestrol.[4] Although the underlying mechanisms remain elusive, our results support the hypothesis that left handedness is related to increased risk of breast cancer.

Contributors: All authors analysed and interpreted the data, critically revised the manuscript, and approved the final version.

What is already known on this topic

High levels of sex hormone in utero may induce left handedness and may change breast tissue as a source for breast cancer

Some case-control studies provide evidence for a relation between left handedness and increased breast cancer risk, but prospective evidence is lacking

What this study adds

Prospective data show an increased risk of premenopausal breast cancer among left handed women

PAHvanN and PHMP conceived and designed the study. SGE, PAHvanN, and PHMP acquired the data. Bernard Slotboom and Bep Verkerk handled and processed the data. MKR, CSPMU, and DEG drafted the manuscript. CSPMU is the guarantor.

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A memorable patient

The "sum" of my fears

I was driving hurriedly to hospital, as I was already a few minutes late after having dropped my son off to school. I could indistinctly hear my passenger, my professor (KPA), cursing me under his breath. I was preoccupied with thoughts of irate patients whom we had called to the outpatients department. I increased my speed to the maximum permissible, 60 km/hour, which was most unusual for me, my usual speed being about 30 km/hour. Indeed, I was the butt of jokes among my colleagues for driving at a snail's pace ("The only way he can meet with an accident is if he gets hit by a cyclist from behind").

As I was driving furiously past the office of the General Officer Commanding-in-Chief, the military policeman stationed there blew his whistle shrilly and waved me to a halt. My worst fears had come true. Now I would be marched up to the commandant for speeding and not observing good order and military discipline. This would entail further delay in the outpatients department and spoil my entire day. Now my professor was visibly and (very) audibly annoyed.

I apologised profusely to the military policeman and started explaining the reasons for speeding, but he simply asked me in a business-like manner to park my car on the curb. As I sheepishly got out of the car, I recognised the policeman as a patient of mine. He had come to me recently for treatment of his pernicious anaemia. He saluted smartly and said that he had not pulled me over because of speeding. Instead, he apologised and explained the real reason: "Sir, you had prescribed vitamin B-12 injections for me. These injections are not available presently, being in short supply. Instead, can I use two injections of vitamin B-6, which is available in the medical stores?"

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