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Risk profile of breast cancer following atypical hyperplasia detected through organized screening

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ABSTRACT

Background: Few population-based data are available indicating the breast cancer risk following detection of atypia within a breast screening program.
Methods: Prospectively collected data from the South Australian screening program were linked with the state cancer registry. Absolute and relative breast cancer risk estimates were calculated for ADH and ALH separately, and by age at diagnosis and time since diagnosis. Post-hoc analysis was undertaken of the effect of family history on breast cancer risk.
Results: Women with ADH and ALH had an increase in relative risk for malignancy (ADH HR 2.81 [95% CI 1.72, 4.59] and (ALH HR 4.14 [95% CI 1.97, 8.69], respectively. Differences in risk profile according to time since diagnosis and age at diagnosis were not statistically significant.
Conclusion: Estimates of the relative risk of breast cancer are necessary to inform decisions regarding clinical management and/or treatment of women with ADH and ALH.

Introduction

Evidence indicates that atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) are risk factors for breast cancer in the general female population [1–3]. However, few population-based data are available to indicate the extent of the increase in breast cancer risk. Further, while much of the available data are based on atypia diagnosed incidentally when women undergo excision biopsies for symptomatic presentations of breast lesions, the majority of atypical lesions are currently detected through screening mammography and the significance of screen-detected ADH or ALH has not been explicitly examined [4,5].

Estimation of the extent of increased risk of breast cancer following atypia is required to inform policies on screening and surveillance intervals for women diagnosed with screen detected ADH or ALH and to plan preventive interventions. If the risk of breast cancer is no different to that among women without ADH/ALH then women can avoid follow-up or surveillance. If the increase in risk is sufficiently high as to warrant surveillance, then it is important to know how frequently, and for what length of time, women should be monitored.

The aim of this study was to estimate the risk of invasive breast cancer or ductal carcinoma in-situ (DCIS) following detection of ADH and ALH in a population-based screening program. Additionally, exploration of the breast cancer risk associated with these lesions was undertaken by time period following diagnosis of the atypia and according to age at diagnosis of the atypia.

Methods

Using a retrospective cohort design, all women who participated in screening at the South Australian breast screening service (BreastScreen SA), between its introduction in 1st January 1989 and 1st December 2010, were included in the study.

The BreastScreen SA database contains records for 272,047 women who attended South Australian screening clinics during the study period. The dataset includes information that is collected from patient information and consent forms completed at each screening episode. Other information recorded includes the results and recommendations of screening mammography and assessment

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procedures, and biopsies; initial surgical treatment details for each episode of treatment; and reasons for discharge from the program. All data are accrued prospectively and audited continuously.

Women were classified according to a screen-detected abnormality and final diagnosis of ADH or ALH after biopsy. The database variable describing the final diagnosis allows one SNOMED term per episode of screening. SNOMED is a system that aids in the systematic recording of data that uses clinical terms. In cases where a woman had multiple lesions detected at a screening episode, the highest risk lesion was recorded using the SNOMED classification system. Women diagnosed with breast cancer within six months of an ADH or ALH diagnosis were considered to have had breast cancer at the time of the initial atypia diagnosis. These women were not classified as having had a preceding ADH or ALH diagnosis but were classified as being free of ADH or ALH and remained in the study as members of the comparison group. For these women, the original date of breast cancer diagnosis was used in the analysis.

The study outcome was development of invasive breast cancer or DCIS, screen-detected or otherwise. For outcome ascertainment in women, who may or may not have continued to participate in screening, the BreastScreen SA database was linked with the South Australian Cancer Registry (SACR), a population-based cancer registry. The data linkage used probabilistic matching, based on full names and dates of birth, with supplementary guidance from residential addresses. It was conducted by experienced staff from the South Australian Health Department Epidemiology Branch. By law, new cases of cancer, with the exception of non-melanoma skin cancer, must be notified to the SACR within one month of diagnosis. Notifications are made by pathology laboratories, hospitals, and radiotherapy departments. Dates of death, irrespective of cause, are also recorded following receipt of information from the Registrar of Births, Deaths and Marriages and linkage with Australia-wide death data from the National Death Index [6].

Censoring of women who migrated out of the state relied on discharge data and other follow-up data from BreastScreen SA records. Electoral data were not readily available for the entire study period but a manual check against the rolls was undertaken for 160 randomly selected women, to check our assumption of minimal subject loss due to out of state migration at the end of the study period [note: registration on the electoral roll is compulsory for all eligible citizens in Australia]. All women but one who had died, were found to be alive and residing in South Australia.

Statistical analysis

Descriptive statistics were calculated for covariates included in the respective models. Differences in distributions between groups were tested by the Pearson chi-squared test, or Fisher's exact test where cell sizes were small, and for ordinal or continuous variables, by the Mann–Whitney U test. Crude incidence rates were calculated to provide an estimate of the absolute risk of breast cancer for women participating in the screening program.

Kaplan–Meier estimates were calculated to provide unadjusted estimates of time-to-event (i.e., breast cancer) following screen-detected ADH or ALH. The log rank and Wilcoxon tests were used to determine the equality of the survival functions for ADH/ALH cases compared to no ADH/ALH (taken from time of entry into the screening program for non ADH/ALH cases). The log rank test places greater weight on later differences in the survival curves, while the Wilcoxon test places greater weight on the earlier differences. Considering both of these tests can be useful in identifying time-varying effects.

Time-to-event analyses, using the Cox Proportional Hazards model, were used to estimate the hazard ratio of breast cancer in the BreastScreen SA cohort, according to whether there was a history of a screen-detected ADH or ALH, respectively.

Study entry was at a woman's first attendance for screening at BreastScreen SA. The final date of follow-up was the 1st December 2010 unless a woman had a breast cancer diagnosis (either screen-detected or otherwise) or had died from causes other than breast cancer before this date, in which case final dates of follow-up were the dates of diagnosis and dates of death respectively.

The proportionality assumption was tested in categorical covariates using plots of the survival function at each level of the variable, plots of the predicted versus observed data points, and plots of the log survival time functions (log–log).

For continuous covariates, proportionality was investigated using Schoenfeld residuals for each covariate [7,8]. Where this assumption was not met (i.e. baseline age), allowance for time varying effects within the model was made by inclusion of interaction terms between the variable and analysis time.

Hazard ratios for breast cancer were calculated for women with and without a history of screen-detected ADH or ALH. Additionally, the risk of breast cancer was estimated for women with ADH or ALH according to the time ($\leq$5 years and >5 years) since ADH/ALH diagnosis and age at diagnosis ($\leq$55 years and >55 years) as a proxy for menopausal status [9].

Australian population-based data indicate that there are higher age-standardized incidence rates for breast cancer in metropolitan areas compared to more remote areas, as well as in higher socio-economic groups [10]. The potential also exists for differences in atypia by socio-economic and geographic areas, although corresponding Australian data are not available. To determine the extent that ADH and ALH contribute to the risk of breast cancer, independently of any potential confounding factors, multi-variable estimates were calculated with adjustment for quintiles of socio-economic status and remoteness of residence, as well as the continuous variables describing age at baseline and the year of a woman's first screen. Socio-economic status and remoteness of residence variables were based on ecological indices incorporating relative disadvantage, and remoteness of area based on road distances from populated geographical locations and services, respectively [11,12].

A post-hoc analysis of breast cancer risk with additional adjustment for a family history of breast cancer was conducted for each model. A family history of breast cancer was defined as applying when a woman had: a first degree relative with breast cancer diagnosed before the age of 50; a first degree relative with bilateral breast cancer diagnosed at any age; or two or more first degree relatives with breast cancer that was diagnosed at any age.

All statistical calculations were performed using Stata version 12.0 [13].

Results

A total of 272, 047 women were included with a median follow up period of 12.2 years (range, 0.003–21.9 years). Initial diagnoses of ADH and ALH occurred in 199 and 57 women, respectively. Disregarding atypias where breast cancers were diagnosed within six months of the atypia, 193 (0.07%) and 56 (0.02%) women were considered to have had a screen-detected ADH or ALH diagnosis, respectively. Descriptive statistics are shown in Table 1 for the women in the BreastScreen SA cohort.

The estimated cumulative absolute risk of subsequent breast cancer in women with a diagnosis of screen-detected ADH was 10.9% [95% CI 7.2%, 16.1%] over a median follow-up period of 12 years (range, 0.003–21.9 years). For women without a diagnosis of ADH or ALH, the absolute risk of breast cancer was 4.1%. For women with ALH, the cumulative absolute risk was 12.5% [95% CI 5.2%,

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