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Breast screening atypia and subsequent development of cancer: observational analysis of the Sloane atypia prospective cohort in England

Freeman K, Jenkinson D, Clements K, Wallis MG, Pinder SE, Provenzano E, Stobart H, Stallard N, Kearins O, Sharma N, Shaaban A, Kirwan CC, Hilton B, Thompson AM, Taylor-Phillips S, on behalf of the Sloane Project Steering Group

Karoline Freeman, Senior Research Fellow, Warwick Screening, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, CV4 7AL, UK.

David Jenkinson, Senior Research Fellow, Warwick Screening, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, CV4 7AL, UK.

Karen Clements, Breast Cancer Research Manager, Screening Quality Assurance Service, NHS England, Birmingham, UK.

Matthew G Wallis, Consultant Radiologist, Cambridge Breast Unit and NIHR Cambridge Biomedical Research Centre, Cambridge University Hospitals NHS Trust, Hills Road. Cambridge, CB2 0QQ UK

Sarah Pinder, Professor of Breast Pathology, School of Cancer & Pharmaceutical Sciences, King's College London, Comprehensive Cancer Centre at Guy's Hospital, King's College London, London, SE1 9RT, UK.

Elena Provenzano, Lead Consultant Breast Pathologist, Histopathology and NIHR Cambridge Biomedical Research Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge, CB2 0QQ, UK.

Hilary Stobart, Patient advocate, Independent Cancer Patients' Voice, http://www.independentcancerpatientsvoice.org.uk

Nigel Stallard, Professor of Medical Statistics and Director of Warwick Clinical Trials Unit, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, CV4 7AL, UK.

Olive Kearins, National Lead Breast Screening QA, Screening Quality Assurance Service, NHS England, Birmingham, UK.

Nisha Sharma, Director of Breast Screening and Clinical Lead for breast imaging, Breast Screening Unit, Seacroft Hospital, York Road, Leeds LS14 6UH, UK.

Abeer Shaaban, Consultant pathologist, University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital Birmingham, Edgbaston, Birmingham, B15 2GW, UK

Cliona Clare Kirwan, Professor of Surgical Trials and Consultant Oncoplastic Breast Surgeon, Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, M20 4BX, UK

Bridget Hilton, National Audit Project Senior QA Officer, Screening Quality Assurance Service, NHS England, Birmingham, UK.

Alastair M Thompson, Section Chief, Breast Surgery, Department of Surgical Oncology, Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, Texas 77005, USA.

Sian Taylor-Phillips, Professor of Population Health, Warwick Screening, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, CV4 7AL, UK.

Correspondence to:

Sian Taylor-Phillips, Warwick Screening, Division of Health Sciences, Warwick Medical School, The University of Warwick, Coventry, CV4 7AL. Email: S.Taylor-Phillips@warwick.ac.uk, ORCID ID: 0000-0002-1841-4346

Abstract

Objective: To explore how the number and type of breast cancers developed following screen-detected atypia compares to the anticipated 11.3 cancers detected per 1000 women screened within one 3-year UK screening round.

Design: Observational analysis of the Sloane atypia cohort, a prospective cohort of women with atypia diagnosed through the UK NHS breast screening programme linked to the English Cancer Registry and the Mortality and Birth Information System for information on subsequent breast cancer and mortality.

Setting: Atypia diagnoses from English breast screening centres reported to the Sloane cohort study.

Participants: 3238 women diagnosed with epithelial atypia between 01/04/2003 and 30/06/2018.

Main outcome measures: Number and type of invasive breast cancers detected at 1-, 3- and 6-years post atypia diagnosis by atypia type, women's age and year of atypia diagnosis.

Results: There was a four-fold increase in detection of atypia after the introduction of digital mammography between 2010 (n=119) and 2015 (n=502). During 19088 person-years of follow-up after atypia diagnosis (until December 2018), 141 women developed breast cancer. Cumulative incidence of cancer per 1000 women with atypia was 0.95 (95% CI 0.28 to 2.7), 14.2 (10.3 to 19.1) and 45.0 (36.3 to 55.1) at one-, three- and six-years post atypia diagnosis. Women diagnosed with atypia more recently were less likely to develop invasive cancer within 3 years (6.0 invasive cancers (3.1 to 10.9) per 1000 women in 2013-2018 versus 24.3 (13.7 to 40.1) and 24.6 (14.9 to 38.3) in 2003-2007 and 2008-2012). Cancers detected were similar to the general screening population regarding grade, size and nodal involvement, with equal numbers ipsilateral and contralateral.

Conclusions Many atypia may represent risk factors rather than precursors of invasive cancer requiring surgery in the short-term. Atypia detected more recently have lower rates of subsequent cancers detected, which may be associated with changes to mammography and biopsy techniques identifying forms of atypia which are more likely to represent overdiagnosis. Annual mammography in the short-term after atypia diagnosis may not be beneficial. More evidence is needed about longer-term risks.

What is already known on this topic

Breast lesions of uncertain malignant potential with atypia may confer a 3-4 times increased long-term risk of subsequent breast cancer.

UK, European and American consensus recommends excision of atypia by vacuum assisted biopsy or open surgery followed by surveillance imaging.

Management with five years of annual surveillance imaging is not evidence based and length, frequency and appropriateness are controversial.

What this study adds

Breast cancer diagnosis within 3 years of atypia was low, particularly in more recent years (since 2012), and may contribute to increased overdiagnosis in breast cancer screening.

More frequent mammography for 5 years after women are diagnosed with atypia may not be beneficial in quality assured breast screening programmes with universal use of digital mammography and vacuum assisted excision of indeterminate lesions, and such surveillance protocols should be reviewed.

There was no evidence that surgical removal of atypia is required to prevent missed cancers; in this cohort vacuum assisted excision appears to be as safe as surgical excision in the management of atypia.

Background

Breast screening programmes aim to identify malignancies early, when treatment is more effective in reducing breast cancer mortality, but also cause overdiagnosis and overtreatment of cancer which would not have presented symptomatically within the person's lifetime.[1] In addition to breast cancer, breast screening programmes also identify an increasing number of lesions of uncertain malignant potential (B3) including those with epithelial atypia. Follow-up of atypia may further contribute to overdiagnosis, therefore current management strategies are controversial.

Atypia refers to the histopathological diagnosis of cytological atypia +/- architectural aberration and is diagnosed in 5% to 10% of needle biopsies performed as part of the English breast screening programme.[2, 3] However, the term atypia includes diverse abnormalities, including atypical ductal hyperplasia (ADH), flat epithelial atypia (FEA) and lobular neoplasia (LN), which includes atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS)). These processes are not malignant themselves, however, cancer can coexist with these lesions [3, 4]. In addition, the presence of atypia has been found to confer a four times increased long-term risk of subsequent breast cancer over a median follow-up of 15.7 years in a meta-analysis of 13 studies including a total of 1759 women.[5] This meta-analysis synthesised mainly small studies (median 92 women) from 1987 to 2010, thus spanning changes to screening programmes, imaging technology, atypia definitions and treatment options, and reported pooled relative risks of cancer development for a range of follow-up from 6.8-21 years, with no study considering short term risk at 3 or 6 years (time periods reflecting NHSBSP further routine screening rounds). While the overall increased risk is apparent, this is of limited use for policy makers in countries where routine screening is available and, in particular, the important question is whether additional mammographic screens for such women are required to detect subsequent cancers earlier.

English guidelines recommend vacuum assisted excision (VAE) for all atypias (except when associated with a papillary lesion which requires assessment of the extent in continuity of the atypia) followed by annual mammographic surveillance.[6] European consensus on the management of B3 lesions with atypia recommends excision by vacuum assisted biopsy (VAB) of FEA and LN, followed by surveillance imaging for 5 years and open surgical excision for ADH.[7] A second and third consensus in 2018 and 2023 stipulated that surveillance can only replace surgical excision of ADH in special situations after discussion at the multi-disciplinary meeting.[8, 9] In the US, surgical excision is recommended for most ADH, for LN where imaging and pathology are discordant and for FEA with ADH. For other atypias, surgical excision is not considered necessary and observation with clinical and imaging follow-up can be offered.[10] Observation and follow-up is not further defined. The recommendations were based on evidence of upgrade rates to cancer on excision and long-term cancer risk. But no evidence on the effectiveness of regular surveillance mammography was available which is of particular importance in countries where routine breast screening is not annual. Annual surveillance imaging is a safety net to ensure no cancers are missed at excision and provide opportunity for early detection in high-risk women, but this is not evidence based; no study has considered cancer detection over the short term, following a diagnosis of any type of atypia or following current diagnostic management. In England for instance, annual surveillance is suggested at present following vacuum-assisted excision of all forms of atypia but with comment that this should be amended as "more data and national guidance become available".[11]

This study presents the first analysis of the English Sloane Project prospective atypia cohort[12] and reports the proportion of women with atypia who develop breast cancer by type of atypia and time-

frame to form the evidence base for policymakers to decide the requirements for surveillance mammography in the first five years after atypia detection.

Methods

Data sources

The Sloane atypia project is a prospective cohort of women with atypia diagnosed through the UK NHS breast screening programme from April 2003 to the present. The dataset is formed from a prespecified prospective data collection form submitted to the Sloane Project, based on pre-set standardised data collection expectations as part of national quality assurance processes. Centre level participation was voluntary, with processes to provide participating centres with a list of eligible cases implemented in recent years to aid participation and completeness of cases.[12] Data included women diagnosed at English breast screening centres only with information on their atypia type, age at diagnosis, mammographic features, biopsy method, histological features, surgical treatment, and adjuvant treatment up until June 2018 (supplementary methods 1.1). Data were matched by NHS number and date of birth at person-level to the English Cancer Registry held by the National Cancer Registration and Analysis Service (NCRAS), and the Mortality and Birth Information System (MBIS) for information on subsequent development of breast cancer and mortality data until December 2018. Data were deidentified before sharing for analysis. The methodology of the Sloane Project data collection, data cleaning and verification is described in detail elsewhere.[13] The present analysis followed our published protocol.[14]

Inclusion criteria

We included all women identified with epithelial atypia in the Sloane database. This included atypical ductal hyperplasia (ADH) or atypical intraductal epithelial proliferation (AIDEP), flat epithelial atypia (FEA), atypical lobular hyperplasia (ALH), and lobular carcinoma in situ (LCIS). Traditional views of the relationship between the different types of atypia are depicted in figure 1 to facilitate understanding how atypia types were considered in the analysis. We combined ALH, LCIS and unspecified LISN/LCIS under the term lobular in situ neoplasia (LISN). The atypia types were defined as described in the supplementary methods 1.2.

+++ Figure 1 +++

Exclusion criteria

The DCIS component of the Sloane Project was excluded from this analysis and has been reported elsewhere.[15-17] We excluded bilateral primary cases where women had DCIS in one breast and atypia in the other or the ”best prognosis” atypia of the bilateral primaries in women with atypia in both breasts; patients where ductal carcinoma in situ (DCIS) was present in addition to the atypia; pleomorphic LCIS (as these are managed akin to DCIS); those with an unknown type of atypia; cases not from England; and women without linkage to MBIS to ascertain vital status on 31st December 2018.

Follow-up

We considered women from six months after their atypia diagnosis until the earliest of death (any cause) or 31 December 2018.

In addition, for the primary analysis follow-up was until the date of the first diagnosis of invasive breast cancer in either breast. For the secondary analysis, follow-up was until the date of the first diagnosis of either DCIS or invasive breast cancer in either breast.

Outcomes

The primary outcome was subsequent invasive breast cancer (see supplementary methods 1.3 for information on collection and definition) per 1000 women diagnosed with atypia at 3 years and 6 years following atypia diagnosis. This was estimated from the cause-specific cumulative incidence function (CIFs) calculated using observed cancer detection and death times. Secondary outcomes included location of subsequent breast cancer; nature of subsequent cancer (grade, size and nodal status), and cancers per 1000 women diagnosed with atypia at 1 year following atypia diagnosis.

Analysis

We summarised the characteristics of women with atypia, characteristics of atypia and histological nature of subsequent cancer events for the whole cohort and by type of atypia using descriptive statistics. We recorded counts of breast cancer at 1 year, 3 years and 6 years and investigated how diagnostic management changed over time and reported the number of deaths from breast cancer (see supplementary methods 1.4 for definition) and deaths from other causes.

For the primary analysis, we calculated cause-specific cumulative incidence functions (CIFs) for invasive breast cancer (combined and split into ipsilateral and contralateral cancers) and death from any cause in a competing risks framework using the survfit function from the R package survival in R 4.1.2.[18] The CIF for invasive cancer was used to estimate the cumulative incidence of invasive cancers at 1 year, 3 years and 6 years, with 95% confidence intervals. The 3- and 6-year time points represented the first and second rounds of screening post atypia diagnosis. The 1-year timepoint was a secondary analysis to explore missed cancers at the time of atypia diagnosis. We repeated the analysis for different types of atypia, age at atypia diagnosis, year of atypia diagnosis and for different diagnostic management strategies to explore their effect on subsequent cancer rates.

For the secondary analysis we considered DCIS as well as invasive breast cancer as the outcome with death as the competing risk at all three timepoints.

We undertook a sensitivity analysis of consecutive cases of atypia only to explore the possibility of selective reporting of atypia cases to the Sloane project, and a sensitivity analysis where we excluded cancers detected within 12 months of atypia diagnosis as missed cancer cases. The justification and approaches for all analyses are reported in the supplementary methods 1.5.

We reported the overall patterns of missing data by recording the number of unrecorded or missing for each variable.

We used flexible parametric models using the method of Hinchliffe and Lambert (2013)[19] to explore the effect of several explanatory variables on the time to event of breast cancer since atypia diagnosis using a competing risks framework and considering events as described above and used this model to produce hazard ratios with 95% CI. We considered age at diagnosis, year of diagnosis, type of atypia, management pathway, calcification and background parenchymal breast density as explanatory variables, and consecutive versus non-consecutive cases. Age was included as a continuous, linear variable (see supplementary methods 1.6 for rationale). We calculated model fit statistics, Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC), for model

selection. A subdistribution model with the same covariates as the chosen model was also fitted (see supplementary methods 1.7 for a discussion of both modelling approaches).

We interpreted results considering significant changes to the breast screening programme and the detection and management of atypia during the study period that were considered relevant (figure 2).

+++ Figure 2 +++

Patient and public involvement

Patients were involved in all stages of the project from grant application through to dissemination. Patients contributed to monthly project meetings, discussion of findings with patient groups and to written reports and publicly available information.

Results

Characteristics of women and their atypia in the Sloane atypia cohort

Between 01/04/2003 and 30/06/2018, 3762 women in the UK with an atypia diagnosis following routine breast screening were reported to the Sloane Project, of whom 3238 met our inclusion criteria (supplementary figure S1 and supplementary table S1). In total, women were reported from 63/77 (81.8%) English breast screening centres, however, this fluctuated over the study period. The mean age of women was 55.6 years (range 46 to 95). The total follow-up for this cohort was 19087.9 person years. Of 3238 women with atypia, 1350 women had ADH, 403 had FEA, 1101 had LISN and 384 had mixed ductal and lobular atypia. Microcalcifications were present in 2525/3238 (78%) of diagnosed atypia.

There was a four-fold increase in the incidence of atypia between 2010 and 2015 (figure 3A) which cannot be explained by the 15% increase in women attending breast screening over the same time period[20] or the change in age of women screened given the two age extensions during the study window. More women with atypia were recorded in the time period 2013 to 2018 (n=2014) than in the previous two time periods (2003 to 2007 n=534 and 2008 to 2012 n=690). This appeared to be a genuine increase in atypia numbers rather than an increase due to more complete reporting, because this increase was also apparent in centres which reported all atypia cases throughout the study period (figure 3B). While an increase in cases of FEA contributed to the overall increase, it was not the sole reason (figure 3A). FEA diagnoses increased over the three time periods proportionately in relation to all atypia cases (2.6% in 2003 to 2007 to 16.8% in 2013 to 2018), while the relative numbers of the other atypia types showed minimal change but with an increase in absolute numbers (Supplementary table S2). The increase in numbers of atypia coincided with an increase in the proportion of atypia with microcalcifications, which was seen around the time when digital mammography was introduced in screening centres, between 2010 and 2013[21] (figure 3A).

+++ Figure 3 +++

Subsequent breast cancer events following diagnosis of atypia

168/3238 (5.2%) women with atypia, with mean follow-up of 5.9 years (range 0.51 to 15.7), developed breast cancer. Of these, 141 were invasive and 27 were DCIS. Invasive cancer characteristics are reported in table 1 for all atypias and separately for each sub-type of atypia. Characteristics of DCIS are reported in supplementary table S3.

Table 1: Characteristics of subsequent invasive cancers (any time after original screening round and up until follow-up) detected following atypia diagnosis

	All atypia	**ADH/AIDEP**	**FEA**	**LISN**	**Mixed ductal and lobular**
Number of women with atypia, n	3238	1350† (41.7)	403 (12.4)	1101 (34.0)	384 (11.9)
Number of women with subsequent breast cancer, n (%)	168 (5.2)*	65 (4.8)	13 (3.2)	60 (5.4)*	30 (7.8)
Subsequent breast cancer: invasive n (%)	141** (83.9)	54 (83.1)	8 (61.5)	54 (90.0)	25‡ (83.3)
Site					
Ipsilateral cancer, n (%)	82 (58.2)	29 (53.7)	4 (50.0)	32 (59.3)	17 (68.0)
Contralateral cancer ,n (%)	59 (41.8)	25 (46.3)	4 (50.0)	22 (40.7)	8 (32.0)
Grade, n (%)					
1	25 (17.7)	9 (16.7)	1 (12.5)	8 (14.8)	7 (28.0)
2	69 (48.9)	27 (50.0)	5 (62.5)	28 (51.9)	9 (36.0)
3	28 (19.9)	15 (27.8)	1 (12.5)	7 (13.0)	5 (20.0)
Unrecorded	19 (13.5)	3 (5.6)	1 (12.5)	11 (20.4)	4 (16.0)
Size in mm					
Median (IQR)	15.0 (9.75; 27.25)	15.0 (10.0; 24.75)	14.0 (13.25; 14.75)	18.0 (10.0; 30.0)	12.0 (8.5; 22.0)
≤20mm, n (%)	77 (54.6)	35 (64.8)	5 (62.5)	23 (42.6)	14 (56.0)
>20mm to ≤50mm, n (%)	32 (22.7)	14 (25.9)	0	13 (24.1)	5 (20.0)
>50mm, n (%)	7 (5.0)	1 (1.9)	1 (12.5)	5 (9.3)	0
Unrecorded, n (%)	25 (17.7)	4 (7.4)	2 (25.0)	13 (24.1)	6 (24.0)
Nodal status n (%)					
0 nodes positive	84 (59.6)	33 (61.1)	5 (62.5)	30 (55.6)	16 (64.0)
1, 2 or 3 nodes positive	22 (15.6)	12 (22.2)	0	6 (11.1)	4 (16.0)
>3 nodes positive	7 (5.0)	3 (5.6)	2 (25.0)	2 (3.7)	0
Unrecorded	28 (19.9)	6 (11.1)	1 (12.5)	16 (29.6)	5 (20.0)
Hormone receptor status n (%)					
Oestrogen receptor (ER) positive	108 (76.6)	39 (72.2)	7 (87.5)	44 (81.5)	18 (72.0)
ER negative	10 (7.1)	8 (14.8)	0	1 (1.9)	1 (4.0)
ER not known / unrecorded	23 (16.3)	7 (13.0)	1 (12.5)	9 (16.7)	6 (24.0)
Progesterone receptor (PgR) positive	47 (33.3)	14 (25.9)	2 (25.0)	21 (38.9)	10 (40.0)
PgR negative	10 (7.1)	5 (9.3)	0	5 (9.3)	0
PgR not known / unrecorded	84 (59.6)	35 (64.8)	6 (75.0)	28 (51.9)	15 (60.0)
HER2 positive	15 (10.6)	5 (9.3)	0	5 (9.3)	5 (20.0)
HER2 negative	89 (63.1)	35 (64.8)	5 (62.5)	36 (66.7)	13 (52.0)

HER2 not known / unrecorded	37 (26.2)	14 (25.9)	3 (37.5)	13 (24.1)	7 (28.0)
Lympho-vascular Invasion n (%)					
Present	12 (8.5)	8 (14.8)	0	3 (5.6)	1 (4.0)
Possible	3 (2.1)	1 (1.9)	0	2 (3.7)	0
Absent	66 (46.8)	29 (53.7)	5 (62.5)	23 (42.6)	9 (36.0)
Not known / unrecorded	60 (42.6)	16 (29.6)	3 (37.5)	26 (48.1)	15 (60.0)

ADH atypical ductal hyperplasia, AIDEP atypical intraductal epithelial proliferation, FEA flat epithelial atypia, LISN Lobular in situ neoplasia

*An additional 2 women had recorded distant metastasis, but no breast cancer recorded.

** This includes one woman with an invasive cancer recorded but no date of detection, who is therefore not included in the analysis of cancer rates at 1-, 3-, and 6-years following atypia diagnosis.

†This includes 326 (10.1%) women who received an AIDEP diagnosis

The characteristics of the subsequent invasive cancers were similar to those of cancers detected in the general screening population. Most of the invasive cancers recorded were ≤20mm and most were node negative. The distribution of grade among all 141 invasive cancers was 25 (17.7%) grade 1, 69 (48.9%) grade 2, 28 (19.9%) grade 3, and 19 (13.5%) unrecorded, which is similar to screen detected cancers in the literature (see supplementary table S4).

The numbers of ipsilateral and contralateral invasive cancers were similar (7.7, 95% CI (4.98 to 11.5) and 6.5, (3.99 to 10.1) cancers per 1000 women at 3 years, respectively). While the reporting of the location for 22 ipsilateral cancers detected within 3 years of the initial atypia diagnosis was incomplete (supplementary table S5), the number of contralateral cancers indicates that many atypia lesions are not direct precursors of subsequent breast cancers within the 15 years of follow-up available for analysis.

Missed cancers at the time of an atypia diagnosis

The number of cancers diagnosed within twelve months is most likely to be reflective of missed cancers at the time of the atypia diagnosis, rather than cancers developing after screening. Within six and twelve months following an atypia diagnosis, 3 invasive cancers were detected in women with atypia; these were one contralateral cancer following an ADH diagnosis and two ipsilateral cancers following a mixed atypia diagnosis. This equates to 0.95 (95% CI 0.28 to 2.7) invasive cancers per 1000 women with atypia.

The main driver for an intensive follow-up of atypia is clinician concern about missing the diagnosis of a cancer when management of atypia moved from diagnostic surgical excision to vacuum-assisted excision (VAE), as a consequence of possible lower volume tissue removal. In the Sloane atypia cohort, the final atypia diagnosis was based on a single diagnostic procedure (standard core biopsy or vacuum assisted biopsy [VAB]) in 477 (14.7%) of women, a second line VAB or VAE in 964 (29.8%) of women and a surgical procedure in 1797 (55.5%) of women. However, management with diagnostic surgical excision decreased and second line VAE increased during the study period (supplementary figure S3), as per UK guidelines.[6] Nevertheless, this change in management strategy had little impact on numbers of invasive cancers detected. Second line VAB/VAE did not result in more cancers missed than surgery at one year (1.08 [0.11 to 5.9] vs 1.12 [0.24 to 3.9] cancers per 1000 women respectively) or three years (9.23 [4.1 to 18.4] vs 18.5 [12.8 to 25.8] cancers per 1000 women respectively). This applied to all atypia types and was independent of the site of cancer (supplementary table S6). The flexible parametric model confirmed that type of management had no effect (Hazard ratio 1.029, 95% CI 0.54 to 1.95, p=0.93 diagnostic surgical excision vs second line VAB/VAE) when added after including age, year and density though the wide confidence interval in this case reflects the considerable uncertainty and means that a reduction in the hazard cannot be ruled out. Thus, few cancers were missed at the time of atypia diagnosis and VAE appears to be as safe as surgical excision in the management of atypia.

Cancers at 3- and 6-years post atypia and long-term risk

Numbers of invasive cancers detected per 1000 women 3 years and 6 years following an atypia diagnosis were estimated using the fitted CIFs to be 14.2 (10.3 to 19.1) and 45.0 (36.3 to 55.1), respectively (based on n=40 and n=94 invasive cancers detected) (figure 4, table 2). While the number of cancers at three years was low, the number was slightly higher at 3.5 years (23.8 [11.4 to

30.3]), which presents a more pragmatic estimate as it includes cancers detected at the first routine (3 yearly) screen after atypia, when not all screens were on time. Numbers of cancers detected at 3, and 6 years after atypia when an invasive cancer or DCIS was the outcome were estimated to be 18.9 (14.3 to 24.5) and 52.8 (43.4 to 63.4) per 1000 women (n=53 and n=113), respectively. Only one woman was reclassified in this analysis as she had a DCIS diagnosis followed by an invasive cancer.

+++ Figure 4 +++

Table 2: Cancers detected for complete study period and for three time periods expressed as counts and estimated from the cumulative incidence function up to 1 year, 3 years, 3.5 years and 6 years post atypia diagnosis

Calendar year at atypia diagnosis	**N atypia cases**	**1 year**		**3 years**		**3.5 years**		**6 years**	
		Absolute number of invasive cancers	**Invasive cancers per 1000 women (95% CI)**	**Absolute number of invasive cancers**	**Invasive cancers per 1000 women (95% CI)**	**Absolute number of invasive cancers**	**Invasive cancers per 1000 women (95% CI)**	**Absolute number of invasive cancers**	**Invasive cancers per 1000 women (95% CI)**
2003-2018	3238	3	0.95 (0.28 to 2.69)	40	14.2 (10.3 to 19.1)	62	23.8 (11.4 to 30.3)	94	45.0 (36.3 to 55.1)
2003-2007	534	0	0	13	24.3 (13.7 to 40.1)	21	39.3 (25.1 to 58.3)	36	67.4 (48.2 to 90.8)
2008-2012	690	2	2.9 (0.61 to 9.94)	17	24.6 (14.9 to 38.3)	24	34.8 (22.9 to 50.4)	40	58.0 (42.2 to 77.1)
2013-2018	2014	1	0.51 (0.055 to 2.89)	10	6.0 (3.09 to 10.9)	17	12.6 (7.5 to 20.0)	18	-

Cancers by age at atypia diagnosis increased with increasing age, apart from the age group 66 to 70 years of age (supplementary table S8). However, when considering age in combination with breast density and year of diagnosis in the flexible parametric model, neither age nor background parenchymal density had a clinically significant impact on cancer detection (supplementary figure S4). Furthermore, atypia type had no major impact on cancers detected (supplementary table S9). Adding atypia type as a variable to the model including age and year of diagnosis did not improve the model fit (supplementary table S13). Results from the models with cause-specific hazards and subdistribution hazards gave the same conclusions (supplement 3). Therefore, there was no evidence that atypia management should be risk stratified by subgroup.

Invasive cancers detected at 3 years were significantly fewer in the last time period (post 2013) compared to the two earlier time periods (estimated to be 6.0, (3.09 to 10.9) vs 24.3, (13.7 to 40.1) and 24.6, (14.9 to 38.3) per 1000 women) and was still low at 3.5 years (12.6, (7.5 to 20.0)). This suggests that the clinical significance of an atypia diagnosed since 2013 was different from the effect of atypia diagnosed in earlier years. This was not due to the lack of follow-up during the latest period (supplementary table S10) or the detection of more FEA in that time period. Excluding women with FEA from the analysis did not remove the observed difference (supplementary table S11). Furthermore, the reduced risk cannot be explained by selective reporting of more severe atypia cases in the earlier time periods, as the reduction in cancer rates was also substantial in an analysis of cases from centres where all consecutive cases were recorded (supplementary table S12). Furthermore, the proportion of non-invasive to invasive breast cancers was higher in the latest time period than in previous time periods.

Taken together, there were more cases of atypia and fewer cancers (but proportionally more DCIS) in the most recent time period (figure 3A).

The cancer risk continued after 6 years (n=46 invasive cancers), in line with previous studies, with potentially slightly higher rates for mixed atypia and lowest rates for FEA at the end of follow-up (figure 3). However, care is needed in projecting long term risk from the earlier years to the more recent atypia cases, which may potentially represent a different spectrum of atypia, and these lack the long-term follow-up available for the former years.

Mode of detection of subsequent breast cancers

57/168 (33.9%) invasive breast cancers and DCIS were detected through screening and 47/168 (28.0%) cancers were detected symptomatically. 32/168 (19.0%) cancers were detected by other outpatient appointments, which may or may not have included annual screens. For 32/168 (19.0%) cancers the mode of detection was not recorded. Mode of detection of subsequent cancers after an atypia diagnosis is depicted in Supplementary figure S5. Other outpatient appointments do not show an annual pattern, suggesting that these cannot be interpreted as detected by annual surveillance mammography. A small number (12/168) of cancers were picked up symptomatically within the first three years post atypia diagnosis.

Discussion

Main findings

In this English Sloane atypia population of 3238 women with any epithelial atypia diagnosis, the incidence of atypia markedly increased from 2012 onwards. At the same time, detection of subsequent breast cancers in women with atypia decreased. Overall, cancer development post atypia was low compared to general population cancer rates and was significantly lower in more recent years than in earlier time periods. We propose that the gradual introduction of digital mammography in England since 2010, which identifies more microcalcifications,[22, 23] may explain a large proportion of the increase in atypia from 2012. This could explain why atypia detected from 2012 onwards had lower rates of subsequent invasive cancers detected. The remaining increase in atypia incidence may be explained by a shift in atypia definitions and pathologists refining their diagnostic criteria, particularly regarding the diagnosis and the terminology of columnar cell lesions, of which flat epithelial atypia is one form, which appears uncommon before 2012. Another factor possibly relating to the increase in atypia could be the increased size of the biopsy needle that may be used in some cases in recent years, increasing the probability of finding atypia, and decreasing the probability of misclassifying atypia as DCIS. It appeared that few cancers were missed at the time of atypia diagnosis and non-surgical management was as safe as surgical excision of atypia in this cohort. The characteristics of cancers detected post atypia were similar to cancers detected in the general screening population and no subgroup was identified that was at increased risk of developing invasive cancer. Therefore, the reporting of atypia at screening may contribute to the problem of overdiagnosis in breast cancer screening.

Comparison with previous studies

This is the first study to look at short-term risk of breast cancer following screen-detected atypia. Previous studies[5, 24-32] are unhelpful in this context or in providing evidence to support a policy on the short-term management of women after an atypia diagnosis as they focus on long-term relative risks and only two studies have investigated atypia in a screening cohort. Boland (2020) reported 4 cancers in 66 screen detected cases of lobular neoplasia after mean follow-up of 62.5 months in Ireland.[27] Castells (2015) reported a cohort of women screened from the Spanish breast screening programme between 1994 and 2011.[31] In 159 women (0.029% of screened women) they recorded proliferative disease with atypia (although this included 28 “benign/uncertain benign” phyllodes tumours in this category, which is perhaps unexpected); of these, six developed breast cancer (invasive or DCIS) which was equivalent to a cancer rate of 8.44/1000 person years compared to 7.7/1000 person years (9.2 considering invasive cancer and DCIS) in our study. In line with the results presented here, Castells concluded that that their results showed an association between benign breast disease and subsequent risk of cancer with only a small number of malignancies misclassified as benign at biopsy and with no impact on cancer risk estimation. Considering all available follow-up (median 6.07 years), Castells (2015) reported an age adjusted risk ratio of 4.56 (95% CI 2.06 to 10.07) for women with atypia when compared to women screened without benign disease (from first screen to cancer diagnosis) but with similar pattern of time to breast cancer in both groups. However, the authors did not report estimates for the first five years post atypia diagnosis. Furthermore, none of the studies included atypia cases detected post 2011 when, according to our results, invasive cancers developed less frequently.

However, changes over time have been previously reported. An increase in lesions of uncertain malignant potential (B3 lesions), together with a decrease in the positive predictive value (PPV) of malignancy for B3 lesions (in particular lobular neoplasia) was reported in 2011 by Rakha et al. who compared B3 lesions detected in 1998-2000 with those detected in 2007-2008.[33] They reported a

decrease in PPV from 35% to 10% for B3 lesions, suggesting as reasons: more accurate targeting of lobular neoplasia lesions by radiologists and identifying more DCIS with VAB which would have been diagnosed as AIDEP on the limited sampling provided by core biopsy.

Strengths and limitations

This Sloane atypia prospective cohort is larger than that included in any predominantly retrospective previous publications or meta-analyses reporting women with atypia and follow-up to cancer. However, the data have some limitations. First, despite the substantial patient numbers, cancer following atypia diagnosis is rare, limiting the statistical power. Second, this is not a complete consecutive cohort across all English breast screening centres for the entire time period, so theoretically atypia lesions which are not included in the Sloane database (which is by voluntary submission) may be systematically different. To explore this, we compared our results for the whole cohort to those for the subset of centres known to have a complete, consecutive sample, and they did not differ. Third, the cohort encompasses a significantly long time period, which is a strength in enabling assessment of temporal changes in the proportion of women who develop cancer. This also, however, complicates interpretation, as several concurrent temporal changes play a role, such as improvement in imaging technology, changes in treatment and management of atypia as well as changes in atypia terminology and definitions and the data collection forms. Fourth, the data lacked information on symptomatic versus screen detected subsequent cancer detection and any data on annual surveillance mammography. We, therefore, know little from the data about how atypia is currently managed, how subsequent cancers were detected and which management strategy may work best in detecting cancers. Finally, the data lacked a comparator to assess cancer risk in a contemporary general screening population to put our findings into context.

Implications for clinical practice

The results suggest that additional annual mammography for the first three years after a diagnosis of epithelial atypia may not be necessary over and above UK standard screening practice (i.e. once every 3 years) offered to all women. The number of women diagnosed with cancer in the first 3 years was low. This cohort was not comparative, so we cannot draw conclusions about the rate of cancers in women with atypia compared to the general screening population. However, the number of cancers detected within 3.5 years (one complete screening round per 1000 women with atypia) was 12.6 (95% CI 7.5 to 20.0) in 2013-2018. In the general population of women who have attended screening aged 50 to 70 years in 2018/19 the total rate of cancers within a 3-year screening round is comparable, at 11.3 per 1000 women (3.5 symptomatically detected interval cancers between screening rounds[34] and 7.8 /1000 detected at the next screening round[20]). Although without statistical comparisons or a matched cohort, this does provide context that suggests the risk of developing cancer in the first 3.5 years is not high for women with atypia diagnosed recently in a quality assured screening programme. The evidence is less clear for extra screening between 3 and 5 years, where the rate of cancer is slightly higher than we would expect (58.0 [42.2 to 77.1] per 1000 women at 6 years after atypia diagnosis); however, this evidence is for atypia diagnoses between 2008 to 2012 before digital mammography was implemented widely and before the expansion in numbers of atypia diagnosis and with the evidence for latter years not yet available. This study provides more limited data for longer term risks, albeit that was not the primary focus. NICE defines the general population risk as having an 11% chance of developing breast cancer in a woman's lifetime with moderate risk as greater than 17% but less than a 30% chance.[35] The 15-year risk in this Sloane cohort was 13.1% for the complete study period, with the caveat that this is less influenced

by more recent atypia diagnoses which have shorter follow-up. However, 63/77 screening centres contributed data to the Sloane atypia cohort which suggests that findings are applicable to screening practice generally in England. Of note, using these findings for policy decision-making in other countries should be carefully considered, with potential differences in breast image acquisition, access to vacuum assisted biopsies, the level of quality assurance of the screening programme and the present management of atypia which may increase the risk of overdiagnosis/over treatment.

Conclusion

Overall, the invasive breast cancer incidence at 3-years after a diagnosis of epithelial atypia was low and, in particular, lower in recent, compared to earlier, years. Few cancers appeared to be missed at the time of an atypia diagnosis. These data, including the similar ipsilateral and contralateral risks, support the concept that many cases of epithelial atypia may represent risk factors rather than precursor lesions for invasive cancer within 15 years of follow-up. Changes to mammography (digital vs plain film) and biopsy techniques (gauge of biopsy needle and use of vacuum assistance) coincide with the reduction in reported subsequent invasive cancers. One possible interpretation may be that more recently 'milder' forms of atypia are detected which are more likely to represent overdiagnosis. Annual mammography in the short-term after atypia diagnosis may not be beneficial and should be reviewed. Previous studies have shown increased longer-term risk of developing cancer with some forms of epithelial atypia, but not all. Even for those lesions with established long-term risk (e.g. ADH, ALH, LCIS), the data presented here indicate that these women would not benefit from enhanced short-term surveillance.

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Figure legend

Figure 1: Overview depicting traditional views of the relationship between different types of ductal and lobular atypia

Black arrows describe the potential ductal and lobular progression pathways. Thinner arrows represent rare progression of ductal precursors to invasive lobular carcinoma (ILC) and lobular precursors to DCIS / invasive carcinoma of no special type (invasive ductal carcinoma – IDC)

FEA - flat epithelial atypia, ADH - atypical ductal hyperplasia, AIDEP - atypical intraductal epithelial proliferation, DCIS – ductal carcinoma in situ, NST - no special type carcinoma, IDC - invasive ductal carcinoma, ALH - atypical lobular hyperplasia, LCIS - lobular carcinoma in situ, LISN - lobular in situ neoplasia, ILC - invasive lobular carcinoma

Figure 2 Significant changes to the screening and management of atypia during the study period (2003-2018)

VAB vacuum assisted biopsy, VAE vacuum assisted excision, FEA flat epithelial atypia, ALH atypical lobular hyperplasia, LCIS lobular cancer in situ, LN lobular neoplasia, ADH atypical ductal hyperplasia, AIDEP atypical intraductal epithelial proliferation

Figure 3: Number of atypia diagnoses by year; A) for all centres by type of atypia and microcalcification present/absent and B) for two centres reporting consecutive cases for the complete study period. A) with proportion of atypia cases with invasive cancer diagnosis within 3.5 years of an atypia diagnosis. (Transition from film-screen to digital mammography occurred in years 2010-2013, FEA became recognised as a histopathological entity in 2013)

Figure 4: Cumulative incidence function for all atypia types and by atypia type for invasive cancer with death from any cause as competing risk

Contributors
KF and STP drafted the manuscript. STP, KC, MGW, SP, EP, HS, NSt, OK, NSh, AMS, AMT, CK contributed to the study conceptualisation and design. KC, BH and OK contributed to data collection. KF and DJ undertook the analysis. All authors commented on the draft, read and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. STP acts as the guarantor.

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Competing interests
All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: KF, DJ, STP, NSt, NSh and SP received funding from the NIHR Research for Patient Benefit Call (RfPB) for the conduct of this study. KF was funded by an NIHR Development and Skills Enhancement award (NIHR302371). STP is funded by the NIHR through a Research Professorship (NIHR302434). EP received a speaker's honoraria and travel costs from Roche to speak at an advisory group meeting. EP participates as a IPB advisor at advisory group meetings. KC is funded as part of the Cancer Grand Challenges PRECISION team (C38317/A24043) which is funded by Cancer Research UK and the Dutch
Cancer Society. HS received travel and support to attend meetings of CRUK Grand Challenge Precision. SP and AMT are members of the PRECISION Consortium, a recipient of a Cancer Research UK Grand Challenge Award, jointly funded by Cancer Research UK and the Dutch Cancer Society (KWF). AMS has participated in Advisory Boards for Exact Sciences and Veracyte. BH, MGW, OK and CCK have nothing to declare.

Ethical approval
This study is classed as audit with no individual patient consent or Ethics Committee approval required. We have received research ethics approval from the University of Warwick Biomedical and Scientific Research Ethics Committee (BSREC 10/20–21, 8 October 2020), Public Health England office for data release approvals (ODR1718_313) and approval from the English Breast Research Advisory Committee (BSPRAC_031). Informed consent from individual participants was not required.

Data Sharing
Data are available upon reasonable request. Access to the Sloane Project data from external parties is governed by application to the breast screening Research Advisory Committee (RAC) and Office for Data Release (ODR). Data will only be released by the Sloane Project to researchers under approval and in an anonymised or depersonalised format and under a data sharing agreement.

Transparency
The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities

The results have already been presented to representatives of appropriate patient groups. After publication, results will be made available through Breast Cancer Now and to the broader public.

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Provenance and peer review
Not commissioned; externally peer reviewed

Figure 1: Overview depicting traditional views of the relationship between different types of ductal and lobular atypia

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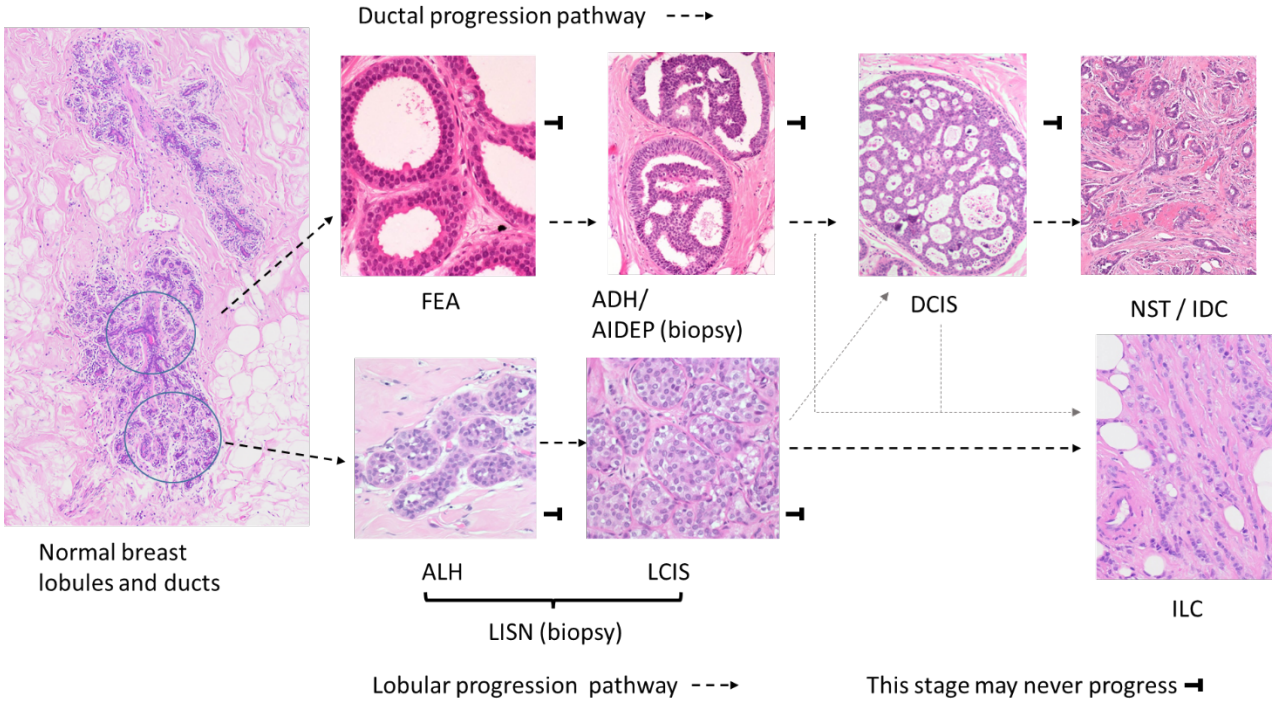
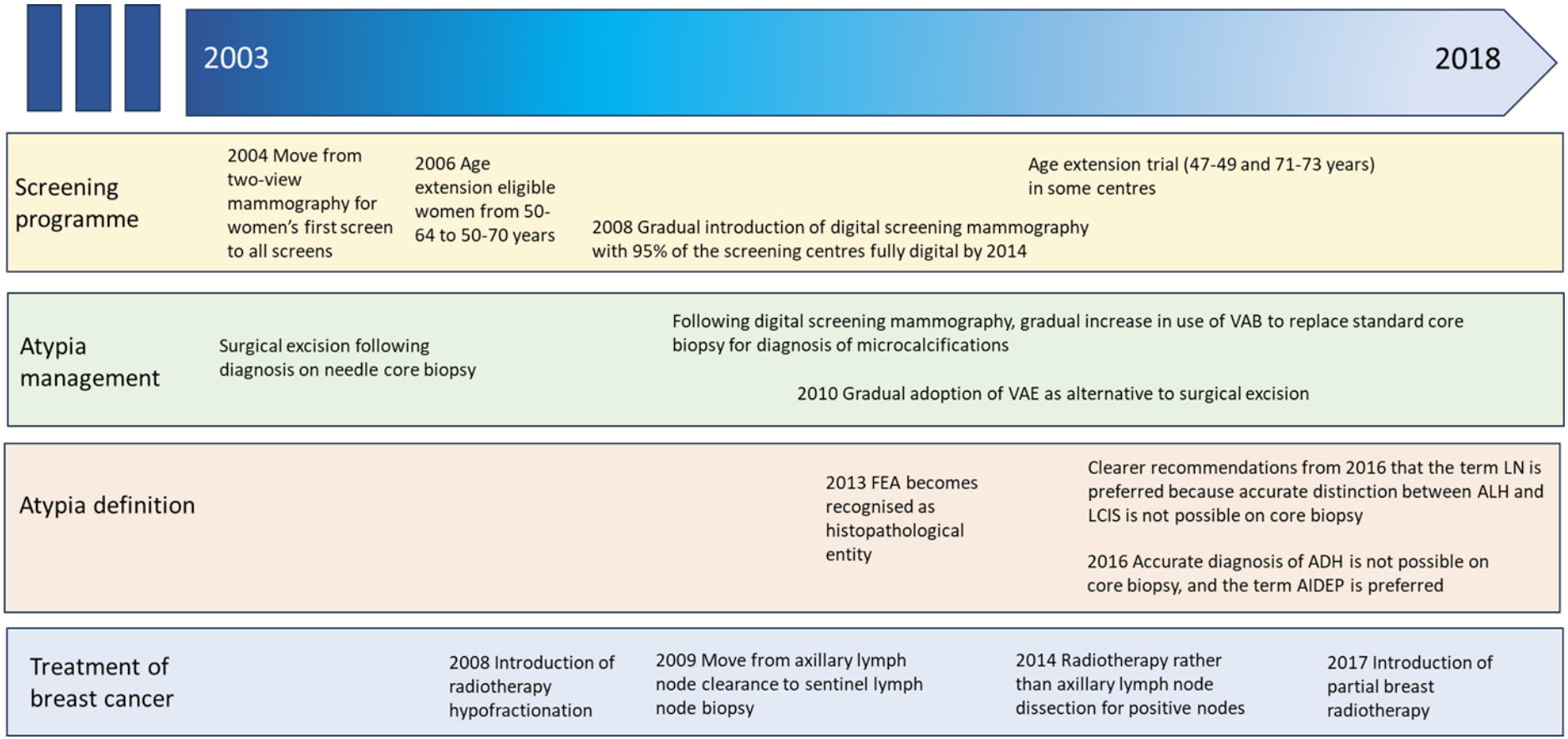


Figure 2 Significant changes to the screening and management of atypia during the study period (2003-2018)



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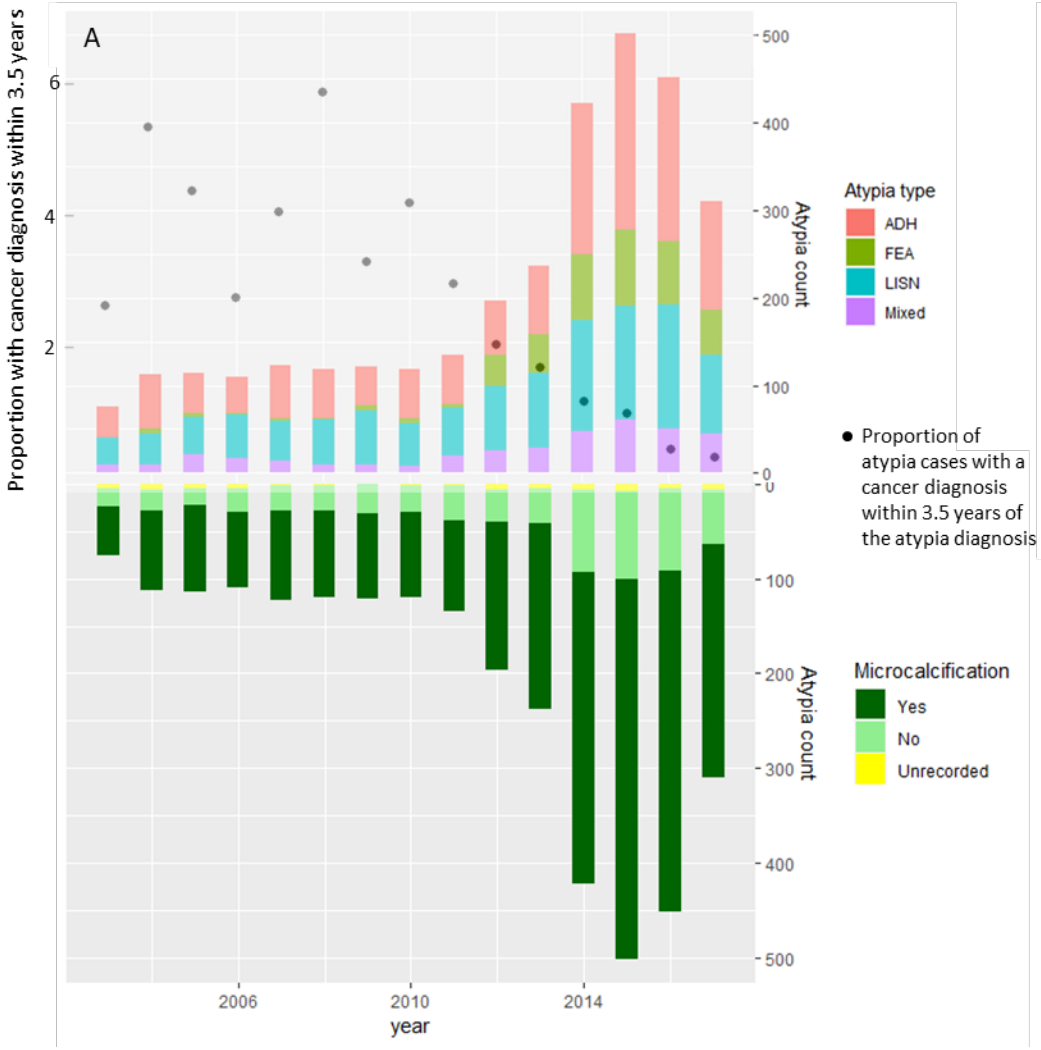


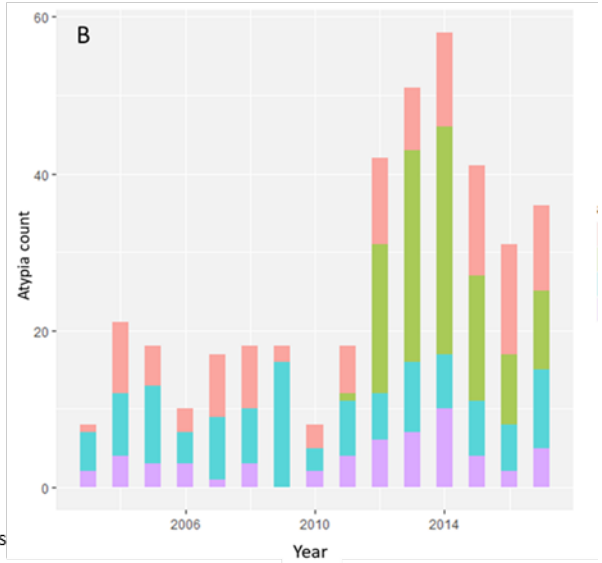
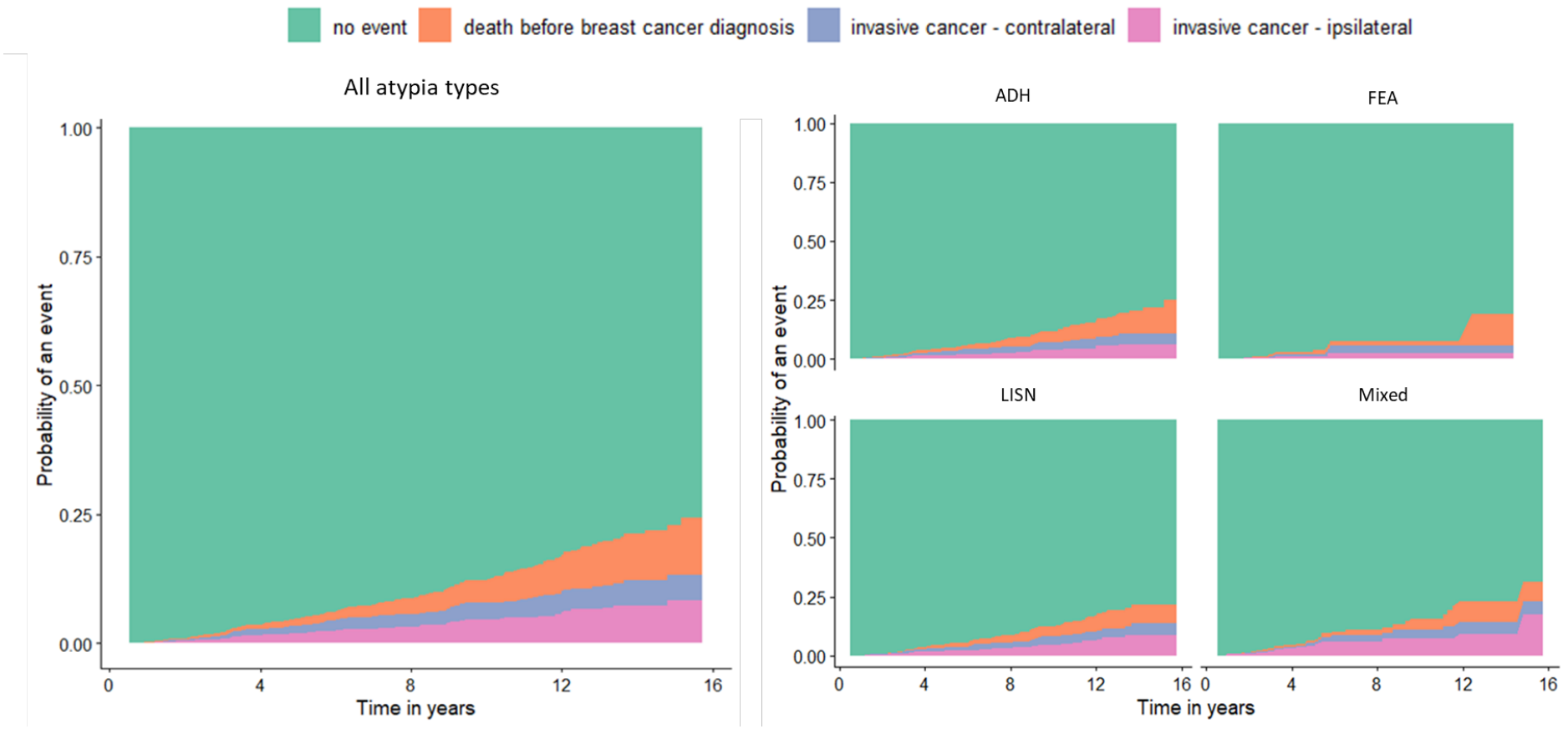


Figure 4: Cumulative incidence function for all atypia types and by atypia type for invasive cancer with death from any cause as competing risk



Supplementary material for Sloane atypia analysis

Content

1. *METHODS*

1.1 Variables received from the Sloane Project data in accordance with the inclusion and exclusion criteria as per the Office for Data Release data sharing contract

Pseudonymised tumour ID
dtmDOD
bytCauseOfDeath
apptdate
intNoOfPreviousScreenings
dtmDateOfMammogram
bytBackgroundPattern
bytPredominantRadiologicalFeature
strLesionMicrocalcification
bytNottinghamDefn
strSizeOfLesionApplicable
dblSIZEOBLDistFromNipple
dblSIZEOBLLengthLesion
dblSIZEOBLDiamLesion
dblSIZECCDistFromNipple
dblSIZECCLengthLesion
dblSIZECCDiamLesion
dblMaxEstimatedLesionSize
bytAgeAtMammogram
bytOperationNumber
OpCount
Op1Date
Op1Procedure
Op1AxNodesTaken
Op1Sentinel
Op1ANS
Op1ANC
Op2Date
Op2Procedure
Op2AxNodesTaken
Op2Sentinel
Op2ANS
Op2ANC
Op3Date
Op3Procedure
Op3AxNodesTaken
Op3Sentinel
Op3ANS
Op3ANC
Op4Date

Op4Procedure
Op4AxNodesTaken
Op4Sentinel
Op4ANS
Op4ANC
Op5Date
Op5Procedure
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Op5Sentinel
Op5ANS
Op5ANC
Op6Date
Op6Procedure
Op6AxNodesTaken
Op6Sentinel
Op6ANS
Op6ANC
ysnCoreBiopsy
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dblOpenBiopsyWeight
ysnTherapeuticExcision
dblTherapeuticExcisionWeight
ysnCavityShaves
dblCavityShavesWeight
ysnImmediateReExcision
dblImmediatereexcisionweight
ysnDelayedReExcision
dbldelayedreexcisionweight
ysnCompletionMastectomy
ysnMastectomy
ysnHISTADH
ysnHISTLISN
ysnSamplesADH
ysnSamplesLISN
intNodesNoExaminedAxilla
intNodesNoPositiveAxilla
intNodesNoExaminedSentinel
intNodesNoPositiveSentinel
intNodesNoExaminedOther
intNodesNoPositiveOther

bytOestrogenReceptorStatus
strOestrogenReceptorStatusCutOff
bytProgesteroneReceptorStatus
strProgesteroneReceptorStatusCutOff
bytHER2ReceptorStatus
strHER2ReceptorStatusCutOff
LngPathologist
ysnCore14GuageDCIS
ysnCore14GuageADH
ysnCore14GuageLCIS
ysnCore14GaugeALH
ysnCore14GaugeFEA
ysnCore14GaugePLCIS
ysnCore14GuageLISN
ysnCore14GaugeAIDEP
ysnCore8_11GuageDCIS
ysnCore8_11GuageADH
ysnCore8_11GuageLCIS
ysnCore8_11GaugeALH
ysnCore8_11GaugeFEA
ysnCore8_11GaugePLCIS
ysnCore8_11GaugeLISN
bytDCISCoreGrade
bytCoreCalcificationPresent
ysnDiseasePresentInSurgicalSpecimenADH
ysnDiseasePresentInSurgicalSpecimenALH
ysnDiseasePresentInSurgicalSpecimenFEA
ysnDiseasePresentInSurgicalSpecimenLCIS
ysnDiseasePresentInSurgicalSpecimenPLCIS
ysnDiseasePresentInSurgicalSpecimenNone
ysnNoSurgicalSpecimen
ysnDiagnosticBiopsy
ysnDiagnosticBiopsyADH
ysnDiagnosticBiopsyLCIS
ysnDiagnosticBiopsyALH
ysnDiagnosticBiopsyFEA
ysnDiagnosticBiopsyPLCIS
ysnDiagnosticBiopsyLISN
ysnDiagnosticBiopsyAIDEP
ysnTheraputicBiopsy
ysnTheraputicBiopsyADH
ysnTheraputicBiopsyLCIS
ysnTheraputicBiopsyALH

ysnTheraputicBiopsyFEA
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ysnTheraputicBiopsyLISN
ysnTheraputicBiopsyAIDEP
ysnAnotherProcessAtMarginALH
ysnAnotherProcessAtMarginFEA
ysnAnotherProcessAtMarginLCIS
ysnAnotherProcessAtMarginPLCIS
ysnAnotherProcessAtMarginADH
ysnAnotherProcessAtMarginLISN
strRadiotherapyExternalBeam
strRadiotherapyExternalBeamNO
ysnAdjvTherapyRadiotherapy
ysnAdjvTherapyOther
ysnAdjvTherapyHormone
ysnAdjvTherapyNoFurther
bytRecurrenceType
dtmRecurrence
ysnDetectFUMammogram
ysnClinicalExamineRoutineFU
ysnGPReferralOPDClinic
ysnOther
strOther
strOther (2)
bytSiteOfDisease
strOtherSiteOfDisease
ysnTypeInvasive
ysntypeNonInvasiveDCIS
ysntypeNonInvasiveLCIS_ALH
bytGradeInvasive
bytGradeDCIS
intSizeDCIS
intSizeInvasive
intSizeWholeTumour
intNodesNumberExamined
intNodesNumberPositive
bytVascularInvasion
bytOestrogenReceptorStatus
strOestrogenReceptorStatusCutOff
bytOestrogenReceptorStatusType
bytProgesteroneReceptorStatus
strProgesteroneReceptorStatusCutOff
bytProgesteroneReceptorStatusType

bytHER2ReceptorStatus
strHER2ReceptorStatusCutOff
bytHER2ReceptorStatusType
ysnProcFWLE
ysnProcMastectomy
ysnProcAxillaryNode
strOtherSurgicalProcedure
ysnRadiotherapy
ysnChemotherapy
ysnHormoneTherapy
bytTypeHormoneTherapy
strOtherHormoneTherapy

Colour code:

	Patient vital status
	Radiology/mammogram
	Surgical and axillary procedures
	Pathology - includes diagnostic/therapeutic pathology
	Adjuvant treatment (i.e. radiotherapy, endocrine therapy, none)
	Recurrence/Further event data

1.2 Atypia types

Atypical Ductal Lesions

For this study we combined AIDEP and ADH in the ADH group. This decision was based on:

1) AIDEP was introduced as a term on the Sloane data collection form in 2019 following the UK national guidelines that the specific entity of ADH should not be diagnosed on standard core biopsy or diagnostic VAB. Therefore, only a small number of cases is expected.

2) Most AIDEP cases that are not upgraded to ductal carcinoma in situ (DCIS) are regarded as ADH on excision.

Lobular Lesions

Lobular neoplasia (LN) and lobular in situ neoplasia (LISN) are interchangeable terms and encompass the spectrum of lobular lesions from atypical lobular hyperplasia (ALH) through to lobular carcinoma in situ (LCIS).

In the UK, guidance is not to record a specific diagnosis of ALH or LCIS on core biopsy or diagnostic VAB because insufficient amounts of material are received to make the distinction with accuracy. Instead, the broader diagnosis of LISN is preferred. This view is reflected in the Sloane pathology data collection form from 2016 onwards.

However, this guidance is not followed consistently, and some pathologists will categorise a lesion as LCIS if they consider there are sufficient changes to make this diagnosis on a core biopsy specimen. Others will (according to the guidelines) classify both ALH and LCIS under the umbrella term LISN, even if there are sufficient features for the atypia to be regarded as LCIS. The term ALH is not used in standard core or VAB reporting, as pathologists classify these as LISN. Thus, whilst the diagnosis of LISN on core biopsy or VAB will include a mixture of cases of ALH and LCIS, if the pathologist has classified the disease as LCIS this is accepted as reliable.

In an excision specimen pathologists will (almost always be able to) distinguish ALH from LCIS, thus ALH diagnoses was derived only from excision specimens.

An LCIS diagnosis may be derived from first diagnostic procedure (if the pathologist has diagnosed it as such) or excision. As a result, LCIS diagnoses were based on a mix of procedures, both core biopsy or VAB or excision specimens, although it is anticipated that the majority were derived from the latter.

Mixed Lesions

Women with atypia can have more than one type of atypia recorded: (a) because types of atypia not infrequently co-exist and may be present in any one specimen, or (b) because different specimens during investigation may result in different diagnoses because some specific diagnoses can only be made on larger volume samples. For the latter reason, the initial diagnoses may, therefore, be revised or specified on excision. Potentially, the initial sampling may remove substantial parts of the lesion resulting in a different diagnosis on subsequent excision.

We used the following three criteria when more than one atypia type was recorded to assign an atypia type for analysis.

a) Use the most specific diagnosis if all forms of atypia present are from either the lobular or ductal group (e.g. ADH rather than AIDEP, ALH rather than LISN);

b) Use the ‘worst’ diagnosis if all diagnoses are from lobular or ductal group. (i.e. ADH>FEA; LCIS>ALH);

c) Use a ‘mixed ductal and lobular’ category for cases where both lobular and ductal atypia co-exist of any category (e.g. ADH & LCIS; LISN & AIDEP etc).

1.3 Collection and definition of cancer events

Cancer events were directly reported by the screening units by retrospective review of a list of atypia patients sent to the centres by the Sloane project up until 2013. After that annual NCRAS extracts were used to link to the Cancer registration data to identify cancer events. Centres were asked to complete a Sloane recurrence form for each event.

Cancer events were ipsilateral breast/nodal or contralateral breast/nodal DCIS or invasive events six months or more after surgical or diagnostic events due to atypia diagnosis.

For women with more than one subsequent cancer event recorded only one event was included in the analysis of cancer rates. In general, the worse diagnosis was considered (i.e. invasive rather than DCIS). In cases with a contralateral and ipsilateral diagnosis on the same date, the contralateral diagnosis was included. In cases with a contralateral and ipsilateral diagnosis on two different dates the earlier diagnosis was included. Women with a DCIS diagnosis followed by invasive cancer diagnosis were handled differently for the primary (outcome is invasive cancer only) and secondary (outcome is the first event of either DCIS or invasive cancer) analysis.

1.4 Definition of cause of death 'breast cancer'

Cause of death data were recorded in the Sloane dataset using rules by the Office for National Statistics that apply the condition or conditions entered in the lowest completed line of Part I of the Medical Certificate Cause of Death (MCCD). For this analysis, a breast cancer death was required to have a record of cause of death 'breast cancer' and a record of a breast cancer event. A cancer event classified 'distant' in conjunction with a breast cancer death was analysed as 'other cancer'.

1.5 Additional analyses

a) Investigation of cancer diagnosis by age at atypia diagnosis

We described the rates at all three time points (1 year, 3 years and 6 years) by age at atypia diagnosis to see if there are any indications of different results for women of different ages.

b) Investigation of temporal effects

The dataset contains women diagnosed with atypia from April 2003 to December 2018. Therefore, there might be some bias due to temporal effects (changes in screening technology, changes in terminology, additional atypia types, changes in diagnostic procedures, treatment and monitoring) resulting in changes in prognosis within any of the atypia types. We investigated temporal effects descriptively by looking at cancer rates for women diagnosed with atypia in different time cohorts of three 5-year periods (using date of atypia diagnosis) and comparing cancer rates and types of cancer detected at the beginning with the end of the cohort.

c) Consecutive cases only

There is some risk of selection bias if clinicians report only more interesting cases of atypia which would preclude generalisability of findings. We explored the data in 5-year intervals comparing atypia type and cancer events from consecutive cases and all cases. The definition for completeness to identify consecutive cases was based on two separate audit events:

A request was sent out to five units on 8th February 2017 to do a retrospective audit looking at patients from 2003-2006. All five units returned data for those years. Therefore, all patients with atypia from these units with a screening diagnosis from 01/04/2003 to 31/03/2006 would be classed as "Unit complete".

In 2019 a list of patients diagnosed with atypia from 01/04/2014 to 31/03/2017 was sent out to all units based on the B3 Crystal Report used by the Association of Breast Surgery (ABS)/NHSBSP Breast

Screening Audit with a covering letter asking for completion of the atypia form for each patient as well as identifying who was ineligible. All patients with atypia with a screening diagnosis 01/04/2014 to 31/03/2017 from units who have returned all of their data forms were classed as “Unit complete”.

In addition, two breast units sent batches of atypia forms for all years and one unit sent atypia for the majority of years. There are emails to confirm this and patients from the units in question were also assigned the category “Unit complete”.

d) Investigation of impact of management strategy

Different levels of investigation (e.g. diagnosis by core biopsy only, VAB or surgical procedure) may have an impact on cancer prognosis. We explored cancer rates following diagnosis of atypia by three levels of management.

The categories of different management levels reflect the size of the sample taken for diagnostic purposes based on the following rationale:

The diagnostic pathway for atypia following a recall from screening typically includes an initial diagnostic procedure (standard core or vacuum assisted biopsy (VAB)), followed by a second diagnostic procedure either surgical excision or a second vacuum assisted specimen. The initial procedure is diagnostic, while the second procedure includes a greater proportion of the lesion for diagnostic purposes and may even excise the whole area. This second VAB is, therefore, referred to as vacuum assisted excision (VAE). A VAE typically includes a larger sample than VAB and a surgical procedure often samples the largest volume. Women with an atypia diagnosis will have had different numbers and types of procedures undertaken along their diagnostic pathway based on the year of their diagnosis (i.e. before or after UK guidelines were published for management of B3 lesions (Pinder et al. 2018)), preference, availability of methods and whether they could technically be sampled by VAE.

The procedures vary in their diagnostic accuracy (because of the difference in amount of tissue received by the pathologist) as well as, potentially, their prognostic ability (as the recurrence rate may be affected by the amount of tissue sampled, and thus the extent of the area of atypia removed, during the investigation process). The three management strategies include women with:

1. Only one initial diagnostic procedure (standard core or VAB);

2. An initial diagnostic procedure (standard core or VAB) and a second vacuum assisted procedure (recorded as a (therapeutic) VAB or VAE) (no surgical procedure);

3. An initial diagnostic procedure (standard core or VAB) and a minimum of one surgical procedure (+/- additional VAB/VAE).

Reference:

Pinder SE, Shaaban A, Deb R, Desai A, Gandhi A, Lee AHS, Pain S, Wilkinson L, Sharma N. NHS Breast Screening multidisciplinary working group guidelines for the diagnosis and management of breast lesions of uncertain malignant potential on core biopsy (B3 lesions). Clin Radiol. 2018;73(8):682-92. doi: 10.1016/j.crad.2018.04.004.

e) Investigation of cancer diagnoses within 1 year of atypia

Cancers typically take longer than 12 months to develop. Cancer diagnoses within 12 months after the atypia diagnosis likely represent missed cancers due to under sampling. We performed an analysis to explore the impact of excluding cancers diagnosed within one year of a diagnosis from the main analysis.

1.6 Options explored how to add age at diagnosis into the model

Four methods of including age at diagnosis were explored: grouped (46 to 55, 56 to 60, 61 to 65, 66 to 70, 71 to 95), continuous linear, continuous linear and quadratic, and a cubic spline. Including age as a continuous, linear term was the best method, having better model fit statistics than the equivalent models for group, linear and quadratic and spline, showing the extra complexity to be unnecessary.

1.7 Flexible parametric model choice – rationale

We analysed time-to-event data with competing risks, considering the first event that happened to each person only; In the main model the competing causes were a diagnosis of invasive breast cancer or death. We also modelled with invasive cancer split into ipsilateral and contralateral, and with invasive cancer and DCIS combined. There are two methods that are used: cause-specific hazards and subdistribution hazards. Putter et al. (2020) gives a succinct summary of the two methods. The cause-specific hazards method models the hazard over time for each cause separately, estimating the hazard of someone who has not yet had an event having an event of that cause. The subdistribution hazards method (Fine and Gray, 1999) evaluates the hazard of an event of the cause of interest amongst those who have yet to have an event of the cause of interest; which it does by including those who have had an event of another cause in with those who have yet to have an event in the "risk set", even though they are unable to have an event of the cause of interest at that time.

The purpose of the analysis may affect the choice of method. Lau et al. (2009) suggest that when looking at the "etiology" of the different causes then cause-specific hazards are better, whereas if trying to predict someone's risk then subdistribution hazards are preferred. We chose to use the cause-specific hazards method, because we wanted to explore how each cause affects the time to event specifically. However, we also decided to run the chosen model in the subdistribution framework, since prediction of a person's risk of an event is an important result for the study. We present the cumulative incidence function from the main model (evaluated at 1 year, 3 years and 6 years after atypia diagnosis) fitted with both cause-specific hazards and subdistribution hazards.

We chose to use the method of Hinchliffe and Lambert (2013b) for our main analysis, which enables us to model a baseline hazard function for each cause separately, each with their own shape. This involves using a dataset where each case is included once for each cause (twice for models with death and invasive cancer and three times when cancer is split into ipsilateral and contralateral). The method was run in Stata using the stpm2 package (Lambert and Royston, 2009). Variables indicating which cause the row relates to were added as main effects and time varying effects with 3 degrees of freedom so that the flexible parametric model can model the baseline hazard for each cause with a restricted cubic spline. The potential explanatory effects were added as main effects on the log cumulative hazard scale, by using scale(hazard) in the stpm2 command. Using the log cumulative hazard scale implies that the variables are being added into the model using proportional hazards.

We plotted Kaplan-Meier survival curves for the event death or invasive cancer (combining the two causes into one) stratified by the groups of each explanatory variable in the chosen model, and found nothing to suggest that assuming proportional hazards was unreasonable. The cause-specific cumulative incidence functions for various values of the explanatory variables in the model were calculated from the model using the postestimation command stpm2cif (Hinchliffe and Lambert, 2013a). The command produces estimates and confidence intervals for the cause-specific cumulative incidence function and the cause-specific hazard function.

A subdistribution hazards model was run using the same covariates as that of the chosen cause-specific hazards model. The model was run in R using the Survival package; using the finegray function to adapt the dataset so that a Fine-Gray model can be run using the coxph function. This used invasive cancer as the event of interest and death as the competing risk, remaining in the "risk set". The cumulative incidence function for invasive cancer was estimated using the survfit function, using the "log-log" type of confidence intervals.

Interpretation of model coefficients in competing risks models.

Austin and Fine (2017) remind that in a competing risks model using cause-specific hazards the model coefficients only tell us about the effect of the explanatory variable on the cause-specific hazard function, and not about its effect on the cumulative incidence function. This is because the cumulative incidence function for each cause is dependent on the cause-specific hazard functions for all causes, not just its own cause. Therefore, care must be taken in interpretating the cause-specific hazards model coefficients. The cause-specific hazard ratios we give show the effect of the explanatory variable on that cause's cause-specific hazard function only.

We have presented the cause-specific cumulative incidence functions for each cause, evaluated at given time points for combinations of values for the three explanatory variables in the model. The effect of each explanatory variable on the cumulative incidence functions can be seen by considering the evaluations in these tables.

Austin and Fine also state that for the subdistribution hazard model the hazard ratio does not show the size of the effect of the explanatory variable on the cumulative incidence function, like it does on the subdistribution hazard function.

Therefore, we advise care when evaluating model coefficients and hazard ratios from competing risks models. For cause-specific hazards models in particular there is no single number that can be used to evaluate the effect of an explanatory variable on the cumulative incidence function.

References

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Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. Am J Epidemiol. 2009 Jul 15;170(2):244-56. doi: 10.1093/aje/kwp107. Epub 2009 Jun 3. PMID: 19494242; PMCID: PMC2732996.

Hein Putter, Martin Schumacher, Hans C. van Houwelingen (2020) On the relation between the cause-specific hazard and the subdistribution rate for competing risks data: The Fine–Gray model revisited. Biometrical Journal. 62:790–807. DOI: 10.1002/bimj.201800274

Jason P Fine and Robert J Gray (1999) “A proportional hazards model for the subdistribution of a competing risk.” Journal of the American Statistical Association, 94:496-509.

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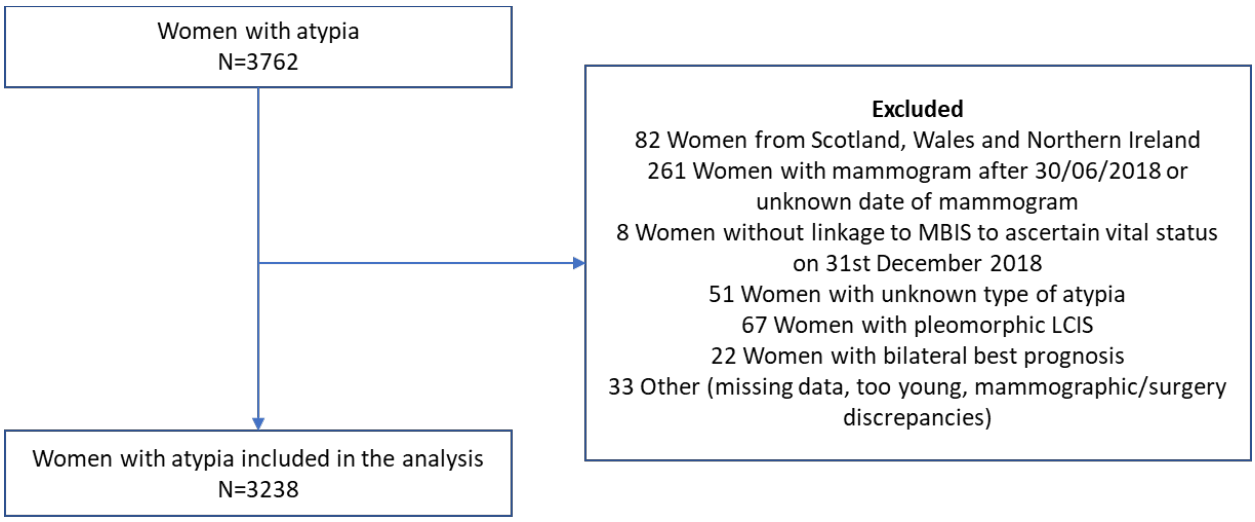
2. RESULTS

2.1 Study population

Figure S1 Flow diagram of study population



2.2 Characteristics of women and their atypia in the Sloane atypia cohort

Table S1 Descriptive statistics of all women with atypia for the study period April 2003 to June 2018

	All atypia	**ADH (including AIDEP)**	**FEA**	**LISN (LN)**				**Mixed ductal and lobular**
				ALH on excision	LCIS (on initial diagnostic procedure or on excision)	LISN unspecified (only LN/LISN reported or ALH on core biopsy)	All LISN	
n (%)	3238	1350* (41.7)	403 (12.4)	77 (2.4)	482 (14.9)	542 (16.7)	1101 (34.0)	384 (11.9)
Age at atypia diagnosis in years								
mean (SD)	55.63 (7.28)	56.55 (7.62)	54.5 (6.98)	55.06 (6.51)	55.03 (7.12)	55.51 (7.17)	55.27 (7.10)	54.58 (6.48)
range	46; 95	46; 95	46; 78	47; 74	46; 83	46; 78	46; 83	46; 81
Number of screening round at which atypia was diagnosed								
median	2.0	2.0	1.0	1.0	1.0	2.0	1.0	1.0
IQR	1.0; 3.0	1.0; 4.0	1.0; 3.0	1.0; 2.5	1.0; 3.0	1.0; 3.0	1.0; 3.0	1.0; 3.0
Range	1.0; 17.0	1.0; 17.0	1.0; 12.0	1.0; 8.0	1.0; 11.0	1.0; 11.0	1.0; 11.0	1.0; 10.0
missing	490	175	101	14	58	78	150	64
Time of follow-up in years								
mean (SD)	5.90 (3.96)	6.0 (4.10)	4.21 (2.50)	5.36 (4.22)	6.37 (3.65)	6.59 (4.32)	6.41 (4.04)	5.83 (4.01)
median	4.42	4.40	3.83	3.91	5.91	4.78	5.32	4.30
IQR	2.86; 8.35	2.86; 8.77	2.52; 5.19	2.40; 6.92	3.50; 8.46	2.86; 10.47	3.07; 9.43	2.73; 7.94
range	0.51; 15.72	0.53; 15.72	0.59; 15.63	0.66; 15.71	0.51; 15.63	0.52; 15.72	0.51; 15.72	0.54; 15.72
Level of management n (%)								
• One diagnostic procedure only (standard core or VAB)	477 (14.7)	143 (10.6)	75 (18.6)	2 (2.6)	100 (20.7)	134 (24.7)	236 (21.4)	23 (6.0)
• Diagnostic procedure plus therapeutic VAB/VAE	964 (29.8)	414 (30.7)	152 (37.7)	24 (31.2)	110 (22.8)	148 (27.3)	282 (25.6)	116 (30.2)
	1797 (55.5)	793 (58.7)	176 (43.7)	51 (66.2)	272 (56.4)	260 (48.0)	583 (53.0)	245 (63.8)

• Diagnostic procedure plus surgical procedure (+/- therapeutic VAB/VAE)								
Management strategy n (%) (not mutual exclusive)								
Diagnostic open biopsy	1488 (46.0)	667 (49.4)	158 (39.2)	44 (57.1)	207 (42.9)	207 (38.2)	458 (41.6)	205 (53.4)
Excision	514 (15.9)	223 (16.5)	25 (6.2)	8 (10.4)	86 (17.8)	103 (19.0)	197 (17.9)	69 (18.0)
Mastectomy	15 (0.5)	0	1 (0.2)	0	5 (1.0)	7 (1.3)	12 (1.1)	2 (0.5)
Multiple operations	55 (1.7)	15 (1.1)	4 (1.0)	0	12 (2.5)	18 (3.3)	30 (2.7)	5 (1.3)
Other surgery	0	0	0	0	0	0	0	0
Axillary surgery	24 (0.7)	5 (0.4)	0	2 (2.6)	3 (0.6)	11 (2.0)	16 (1.5)	3 (0.8)
Endocrine treatment	19 (0.6)	1 (0.1)	0	1 (1.3)	6 (1.2)	9 (1.7)	16 (1.5)	2 (0.5)
Radiotherapy	6 (0.2)	3 (0.2)	0	0	2 (0.4)	1 (0.2)	3 (0.3)	0
Radiotherapy (unrecorded)	3 (0.1)	0	1 (0.2)	0	2 (0.4)	0	2 (0.2)	0
Other therapy	6 (0.2)	6 (0.4)	0	0	0	0	0	0
No surgery	1444 (44.6)	559 (41.4)	227 (56.3)	26 (33.8)	210 (43.6)	282 (52.0)	518 (47.0)	140 (36.5)
No further adjuvant therapy	3103 (95.8)	1237 (91.6)	402 (99.8)	76 (98.7)	474 (98.3)	532 (98.2)	1082 (98.3)	382 (99.5)
Surgical procedure not specified	0	0	0	0	0	0	0	0

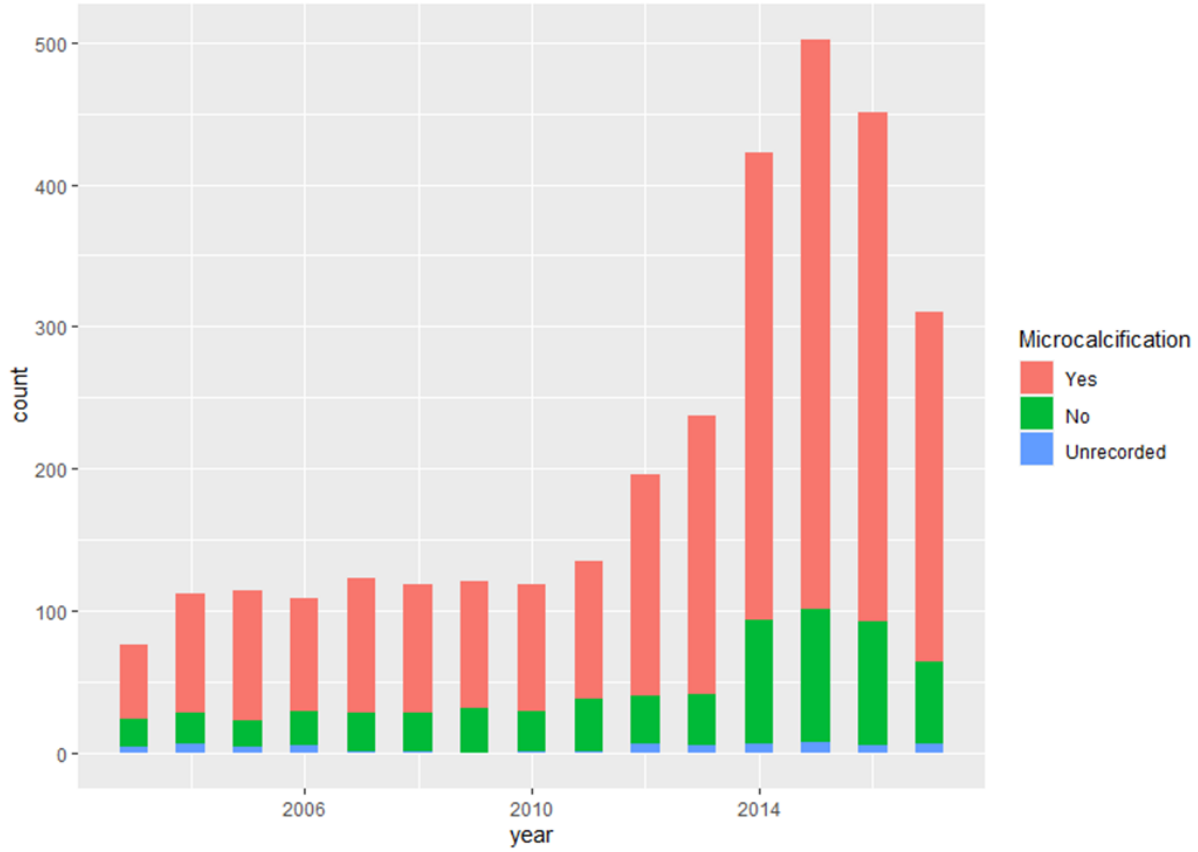
*This includes 326 (10.1%) women who received an AIDEP diagnosis without an ADH diagnosis

Table S2 Number of women with atypia and characteristics of subsequent cancers detected following atypia diagnosis by atypia type for three time periods separately

	All atypia	**ADH**	**FEA**	**LISN (LN)**				**Mixed ductal and lobular**
				ALH on excision	**LCIS**	**LISN unspec**	**All LISN**	
2003 to 2007								
Number of women with atypia n (%)	534	244 (45.7)	14 (2.6)	12 (2.2)	67 (12.5)	127 (23.8)	206 (38.6)	70 (13.1)

Number of women with a cancer detected n (%)	88 (16.5)	30 (12.3)	3 (21.4)	3 (25.0)	11 (16.4)	24 (18.9)	38 (18.4)	17 (24.3)
Invasive cancer n (%)	75 (85.2)	26 (86.7)	3 (100)	3 (100)	9 (81.8)	19 (79.2)	31 (81.6)	15 (88.2)
Non-invasive cancer (DCIS) n (%)	9 (10.2)	4 (13.3)	0	0	1 (9.1)	3 (12.5)	4 (10.5)	1 (5.9)
2008 to 2012								
Number of women with atypia n (%)	690	276 (40.0)	50 (7.2)	10 (1.4)	172 (24.9)	109 (15.8)	291 (42.2)	73 (10.6)
Number of women with a cancer detected n (%)	53 (7.7)	23 (8.3)	1 (2.0)	2 (20.0)	10 (5.8)	9 (8.3)	21 (7.2)	8 (11.0)
Invasive cancer n (%)	47 (88.7)	19 (82.6)	1 (100)	2 (100)	9 (90.0)	9 (100)	20 (95.2)	7 (87.5)
Non-invasive cancer (DCIS) n (%)	6 (11.3)	4 (17.4)	0	0	1 (10.0)	0	1 (4.8)	1 (12.5)
2013 to 2018								
Number of women with atypia n (%)	2014	830 (41.2)	339 (16.8)	55 (2.7)	243 (12.1)	306 (15.2)	604 (30.0)	241 (12.0)
Number of women with a cancer detected n (%)	32 (1.6)	12 (1.4)	9 (2.7)	0	2 (0.8)	3 (1.0)	5 (0.8)	6 (2.5)
Invasive cancer n (%)	19 (59.4)	9 (75.0)	4 (44.4)	0	2 (100)	1 (33.3)	3 (60.0)	3 (50.0)
Non-invasive cancer (DCIS) n (%)	12 (37.5)	3 (25.0)	5 (55.6)	0	0	1 (33.3)	1 (20.0)	3 (50.0)

Figure S2 Number of atypia with microcalcifications present or absent by year



2.3 Subsequent events following atypia

Table S3 Characteristics of subsequent invasive and non-invasive cancers by atypia type and number of deaths

	All atypia	ADH/AIDEP	FEA	LISN (LN)				Mixed ductal and lobular
				ALH on excision	LCIS	Unspecified LISN	All LISN	
Number of women n	3238	1350† (41.7)	403 (12.4)	77 (2.4)	482 (14.9)	542 (16.7)	1101 (34.0)	384 (11.9)
Number of women with breast cancer n (%)	168 (5.2)*	65 (4.8)	13 (3.2)	5 (6.5)	22 (4.6) (*)	33 (6.1) (*)	60 (5.4)*	30 (7.8)
Deaths from breast cancer n (%)	10‡ (5.8)	3 (4.6)	0	0	3 (13.6)	3† (9.1)	6‡ (10.0)	1 (3.3)
Deaths from other causes in breast cancer women								
Other cancer n (%)	1 (0.6)	0	0	0	0	0	0	1 (3.3)
Non-cancer n (%)	3 (1.7)	1 (1.5)	0	1 (20.0)	0	1 (3.0)	2 (3.3)	0
Cancer (unknown type) n (%)	1 (0.6)	1 (1.5)	0	0	0	0	0	0
Deaths from other causes in atypia women								
Other cancer n (%)	35 (20.2)	18 (27.7)	1 (7.7)	1 (20.0)	2 (9.1)	8 (24.2)	11 (18.3)	5 (16.7)
Non-cancer n (%)	51 (29.5)	24 (36.9)	4 (30.8)	2 (40.0)	7 (31.8)	9 (27.3)	18 (30.0)	5 (16.7)
Cancer (unknown type) n (%)	2 (1.2)	1 (1.5)	0	0	1 (4.5)	0	1 (1.7)	0
Invasive cancer n (%)	141** (83.9)	54 (83.1)	8 (61.5)	5 (100)	20 (90.9)	29 (87.9)	54 (90.0)	25** (83.3)
Site								
Ipsilateral cancer n (%)	82 (58.2)	29 (53.7)	4 (50.0)	3 (60.0)	12 (60.0)	17 (58.6)	32 (59.3)	17 (68.0)
Contralateral cancer n (%)	59 (41.8)	25 (46.3)	4 (50.0)	2 (40.0)	8 (40.0)	12 (41.4)	22 (40.7)	8 (32.0)
Grade n (%)								
1	25 (17.7)	9 (16.7)	1 (12.5)	2 (40.0)	3 (15.0)	3 (10.3)	8 (14.8)	7 (28.0)
2	69 (48.9)	27 (50.0)	5 (62.5)	2 (40.0)	12 (60.0)	14 (48.3)	28 (51.9)	9 (36.0)
3	28 (19.9)	15 (27.8)	1 (12.5)	1 (20.0)	2 (10.0)	4 (13.8)	7 (13.0)	5 (20.0)
Unrecorded	19 (13.5)	3 (5.6)	1 (12.5)	0	3 (15.0)	8 (27.6)	11 (20.4)	4 (16.0)
Size in mm								
Mean (SD)	21.17 (18.33)	19.76 (16.40)	30.67 (43.83)	11.67 (3.76)	27.39 (20.57)	20.85 (13.74)	23.05 (17.05)	17.84 (13.38)
Median	15.0	15.0	14.0	10.0	19.0	19.5	18.0	12.0
IQR	9.75; 27.25	10.0; 24.75	13.25; 14.75	9.5; 13.0	11.25; 46.0	10.25; 28.0	10.0; 30.0	8.5; 22.0
Range	3.0; 120.0	3.0; 100.0	8.0; 120.0	9.0; 16.0	5.0; 70.0	4.0; 59.0	4.0; 70.0	4.0; 46.0
≤20mm n (%)	77 (54.6)	35 (64.8)	5 (62.5)	3 (60.0)	10 (50.0)	10 (34.5)	23 (42.6)	14 (56.0)
>20mm to ≤50mm n (%)	32 (22.7)	14 (25.9)	0	0	4 (20.0)	9 (31.0)	13 (24.1)	5 (20.0)

>50mm n (%)	7 (5.0)	1 (1.9)	1 (12.5)	0	4 (20.0)	1 (3.4)	5 (9.3)	0
Unrecorded n (%)	25 (17.7)	4 (7.4)	2 (25.0)	2 (40.0)	2 (10.0)	9 (31.0)	13 (24.1)	6 (24.0)
Nodal status n (%)								
0 nodes	84 (59.6)	33 (61.1)	5 (62.5)	3 (60.0)	13 (65.0)	14 (48.3)	30 (55.6)	16 (64.0)
1,2 or 3 nodes	22 (15.6)	12 (22.2)	0	0	2 (10.0)	4 (13.8)	6 (11.1)	4 (16.0)
>3 nodes	7 (5.0)	3 (5.6)	2 (25.0)	0	2 (10.0)	0	2 (3.7)	0
Unrecorded	28 (19.9)	6 (11.1)	1 (12.5)	2 (40.0)	3 (15.0)	11 (37.9)	16 (29.6)	5 (20.0)
Hormone receptor status n (%)								
Estrogen positive	108 (76.6)	39 (72.2)	7 (87.5)	4 (80.0)	19 (95.0)	21 (72.4)	44 (81.5)	18 (72.0)
Estrogen negative	10 (7.1)	8 (14.8)	0	0	0	1 (3.4)	1 (1.9)	1 (4.0)
Estrogen not known / unrecorded	23 (16.3)	7 (13.0)	1 (12.5)	1 (20.0)	1 (5.0)	7 (24.1)	9 (16.7)	6 (24.0)
Progesteron positive	47 (33.3)	14 (25.9)	2 (25.0)	3 (60.0)	10 (50.0)	8 (27.6)	21 (38.9)	10 (40.0)
Progesteron negative	10 (7.1)	5 (9.3)	0	1 (20.0)	0	4 (13.8)	5 (9.3)	0
Progesteron not known / unrecorded	84 (59.6)	35 (64.8)	6 (75.0)	1 (20.0)	10 (50.0)	17 (58.6)	28 (51.9)	15 (60.0)
HER-2 positive	15 (10.6)	5 (9.3)	0	0	3 (15.0)	2 (6.9)	5 (9.3)	5 (20.0)
HER-2 negative	89 (63.1)	35 (64.8)	5 (62.5)	4 (80.0)	16 (80.0)	16 (55.2)	36 (66.7)	13 (52.0)
HER-2 not known / unrecorded	37 (26.2)	14 (25.9)	3 (37.5)	1 (20.0)	1 (5.0)	11 (37.9)	13 (24.1)	7 (28.0)
Non-invasive cancer (DCIS) n (%)	27 (16.1)	11 (16.9)	5 (38.5)	0	2 (9.1)	4 (12.1)	6 (10.0)	5 (16.7)
Site								
Ipsilateral n (%)	20 (47.1)	9 (81.8)	3 (60.0)	0	2 (100.0)	2 (50.0)	4 (66.7)	4 (80.0)
Contralateral n (%)	7 (25.9)	2 (18.2)	2 (40.0)	0	0	2 (50.0)	2 (33.3)	1 (20.0)
Grade n (%)								
1	4 (14.8)	2 (18.2)	1 (20.0)	0	0	1 (25.0)	1 (16.7)	0
2	6 (22.2)	4 (36.4)	1 (20.0)	0	0	1 (25.0)	1 (16.7)	0
3	12 (44.4)	4 (36.4)	3 (60.0)	0	1 (50.0)	1 (25.0)	2 (33.3)	3 (60.0)
Unrecorded	5 (18.5)	1 (9.1)	0	0	1 (50.0)	1 (25.0)	2 (33.3)	2 (40.0)
Size in mm								
Mean (SD)	16.62 (17.02)	13.75 (9.74)	NA	NA	NA	27.0 (37.32)	27.75 (30.51)	9.67 (9.61)
Median	10.0	10.0	NA	NA	NA	8.0	19.0	8.0
IQR	7.0; 20.0	7.0; 15.5	NA	NA	NA	5.5.; 39.0	6.75; 40.0	4.5; 14.0
Range	1.0; 70.0	7.0; 35.0	NA	NA	NA	3.0; 70.0	3.0; 70.0	1.0; 20.0
≤20mm n (%)	13 (48.1)	7 (63.6)	1 (20.0)	0	0	2 (50.0)	2 (33.3)	3 (60.0)
>20mm to ≤50mm n (%)	2 (7.4)	1 (9.1)	0	0	1 (50.0)	0	1 (16.7)	0
>50mm n (%)	1 (3.7)	0	0	0	0 (	1 (25.0)	1 (16.7)	0
Unrecorded n (%)n (%)	11 (40.7)	3 (27.3)	4 (80.0)	0	1 (50.0)	1 (25.0)	2 (33.3)	2 (40.0)

*An additional 2 women had a recorded distant cancer, but no breast cancer recorded.

** This includes one woman with an invasive cancer recorded but no date of detection, who is therefore not included in the analysis of cancer rates at 1, 3, and 6 years following atypia diagnosis.

†This includes 326 (10.1%) women who received an AIDEP diagnosis without an ADH diagnosis

‡No death certificate only breast cancer death occurred, however, one additional woman with a distant cancer but no record of a breast cancer had breast cancer as cause of death

Table S4 Distribution of grade for subsequent invasive cancers compared to published figures

	All invasive cancers (n=141)	Cancers within 3 years (n=40)	Screen detected (Allgood 2011*) (n=7737)	Symptomatic detected (Allgood 2011*) (n=11674)
Grade 1	25 (17.7%)	5 (12.5%)	2045 (26.4%)	1099 (9.4%)
Grade 2	69 (48.9%)	18 (45.0%)	3038 (39.3%)	2719 (23.3%)
Grade 3	28 (19.9%)	9 (22.5%)	1327 (17.2%)	3898 (33.4%)
Unrecorded	19 (13.5%)	8 (20.0%)	1327 (17.2%)	2958 (25.3%)

*Allgood PC, Duffy SW, Kearins O, O'Sullivan E, Tappenden N, Wallis MG, Lawrence G. Explaining the difference in prognosis between screen-detected and symptomatic breast cancers. Br J Cancer. 2011 May 24;104(11):1680-5. doi: 10.1038/bjc.2011.144.

Table S5 Location of 22 ipsilateral invasive cancers 3 years post atypia diagnosis by atypia type

		ADH	**FEA**	**LISN**	**Mixed**
Location of subsequent invasive cancer	At or adjacent to site of atypia	3	0	3	2
	Some distance from atypia	1	0	1	0
	Other	0	0	0	0
	Unrecorded	4	2	3	3

2.4 Missed cancers at atypia diagnosis

Figure S3 Proportion of diagnostic management options performed by year

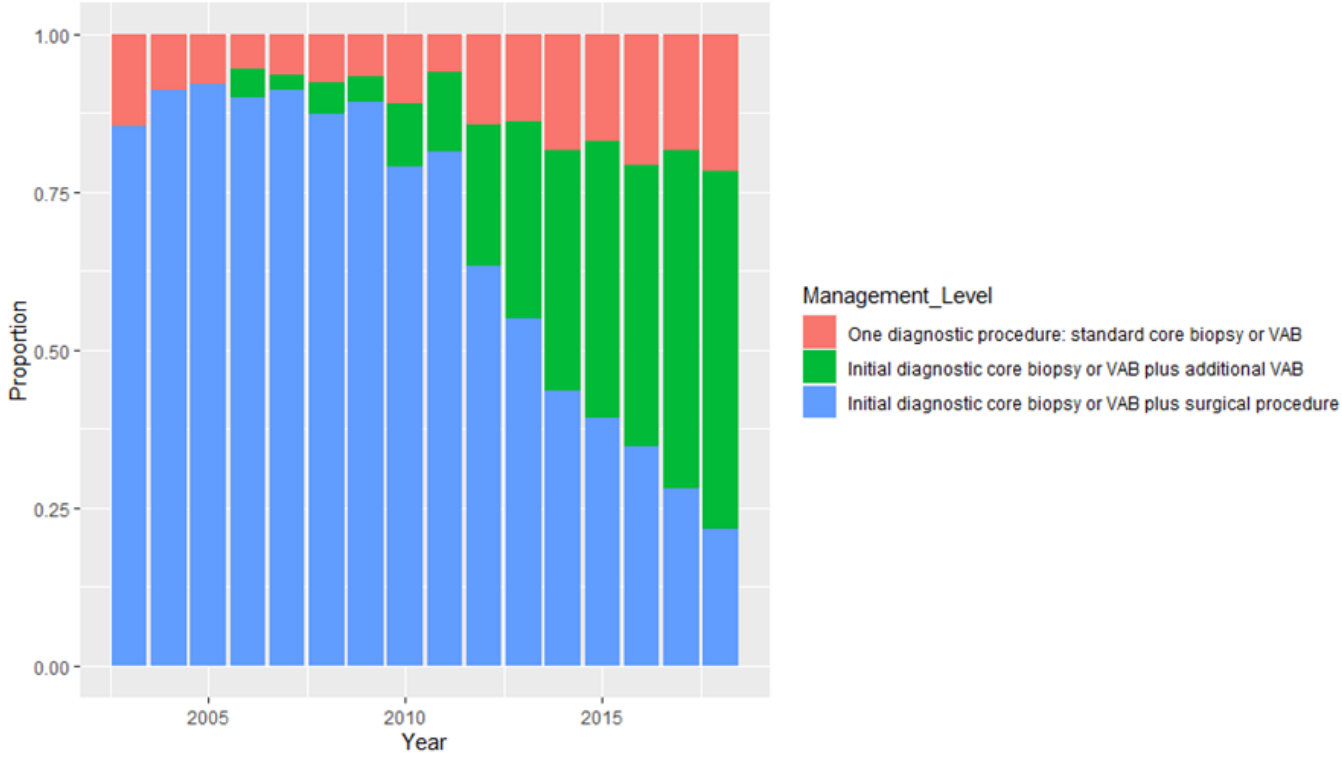


Table S6 Invasive cancers per 1000 women with atypia at 1 year and 3 years post atypia diagnosis estimated from CIF by management strategy and site of invasive cancers separately for atypia types

	Cancers per 1000 women at 1 year		**Cancer per 1000 women at 3 years**	
	Ipsilateral	**Contralateral**	**Ipsilateral**	**Contralateral**
Following a diagnosis of ADH				
'Diagnostic' needle biopsy only with no second procedure	0	0	0	0
Second line vacuum biopsy/excision and no surgery	0	2.54 (0.25,13.5)	5.95 (1.21,20.1)	5.83 (1.18,19.8)
Management involves diagnostic surgical excision	0	0	8.21 (3.45,17.1)	8.08 (3.4,16.9)
Following a diagnosis of FEA				
'Diagnostic' needle biopsy only with no second procedure	0	0	0	0
Second line vacuum biopsy/excision and no surgery	0	0	7.87 (0.711,39.3)	10.10 (0.893,49.7)
Management involves diagnostic surgical excision	0	0	6.54 (0.601,33)	0
Following a diagnosis of LISN				
'Diagnostic' needle biopsy only with no second procedure	0	0	9.89 (1.96,32.8)	0
Second line vacuum biopsy/excision and no surgery	0	0	0	3.91 (0.374,20.3)
Management involves diagnostic surgical excision	0	0	8.83 (3.38,19.6)	11.10 (4.64,23)
Following a diagnosis of mixed atypia				
'Diagnostic' needle biopsy only with no second procedure	0	0	0	0
Second line vacuum biopsy/excision and no surgery	0	0	0	0
Management involves diagnostic surgical excision	8.26 (1.67,27.4)	0	21.80 (8.23,47.4)	8.56 (1.73,28.4)

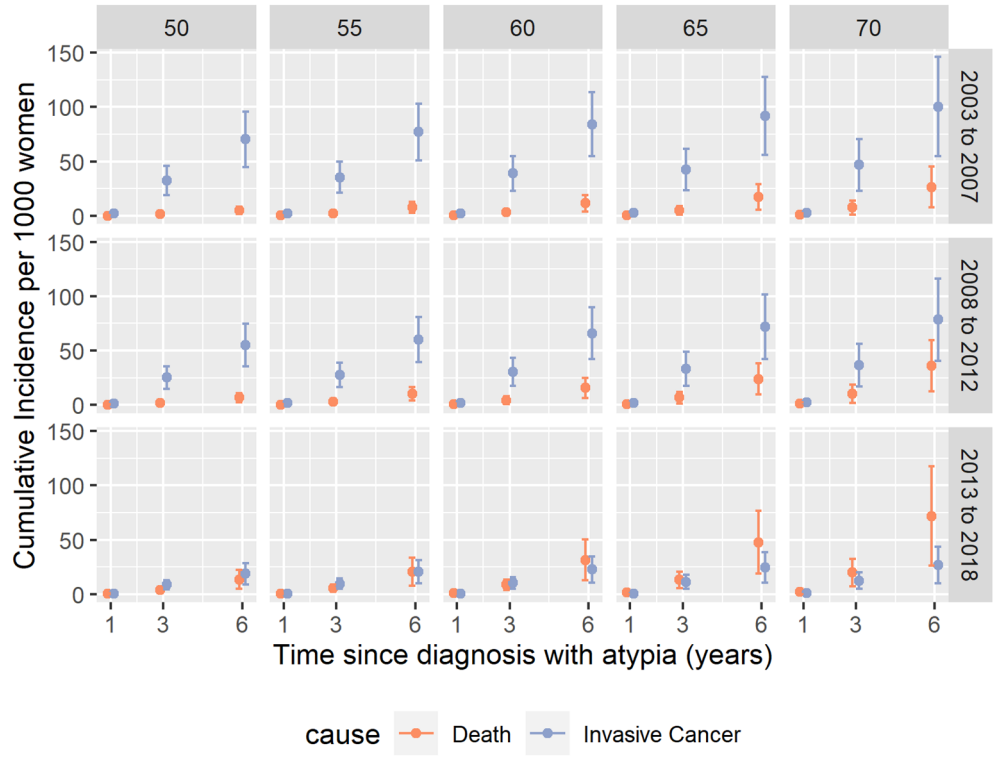
2.5 Cancers at 3- and 6-years post atypia and long-term risk

Table S8 Invasive cancer rates per 1000 women with atypia at 1 year, 3 years and 6 years post atypia diagnosis by age group estimated from CIF

Age at atypia diagnosis	**1 year**	**3 years**	**6 years**
≤55 years	1.03 (0.222,3.6)	9.82 (5.95,15.4)	39.8 (29.3,52.7)
56 to 60 years	0	20.4 (9.61,38.3)	60.3 (36.2,92.9)
61 to 65 years	2.91 (0.284,15.3)	26.2 (12.3,49)	66.3 (38.7,104)
66 to 70 years	0	6.28 (1.28,21)	24.4 (9.94,50.1)
>70 years	0	52 (19.2,109)	64.9 (26.3,128)

Figure S4. Cumulative incidence function for invasive cancer and death from the main model, evaluated at 1 year, 3 years, and 6 years since diagnosis with atypia; by age at diagnosis, year of diagnosis and women's breast background parenchymal density (high figure 3a, low figure 3b).

a
High density



b
Low density

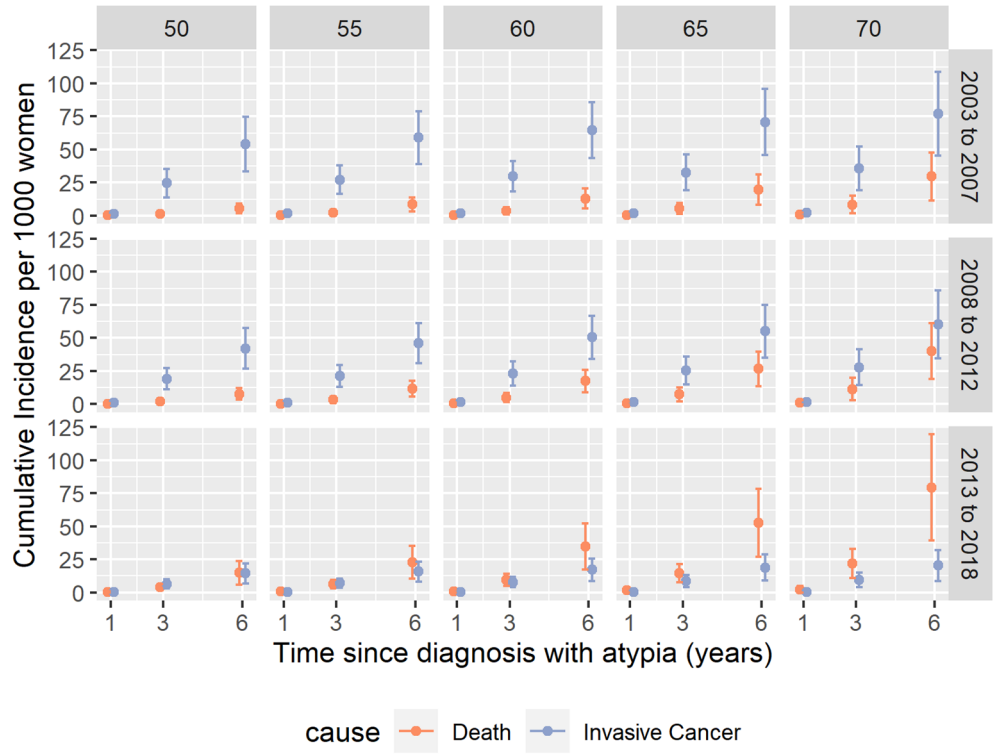


Table S9 Invasive cancer rates at 3 years post atypia by atypia type estimated from CIF

	ADH	FEA	LISN	Mixed
Invasive cancer per 1000 women with atypia (95% CI)	13.6 (8.1,21.6)	9.47 (2.62,25.9)	14.3 (8.23,23.5)	20.8 (9.21,40.6)

Table S10 Invasive cancer rates at 1 year, 3 years and 6 years post atypia diagnosis per 1000 women estimated from CIF for 3 time periods under different scenarios

Calendar year at atypia diagnosis	N atypia cases	1 year		3 years		6 years	
		Cancer cases	Cancers per 1000 women (95% CI)	Cancer cases	Cancers per 1000 women (95% CI)	Cancer cases	Cancers per 1000 women (95% CI)
2003-2018	3238	3	0.95 (0.28,2.69)	40	14.2 (10.3,19.1)	94	45.0 (36.3,55.1)
2003-2007	534	0	0	13	24.3 (13.7, 40.1)	36	67.4 (48.2, 90.8)
2008-2012	690	2	2.9 (0.61, 9.94)	17	24.6 (14.9, 38.3)	40	58.0 (42.2, 77.1)
2013-2018	2014	1	0.51 (0.055, 2.89)	10	6.0 (3.09, 10.9)	18	-
2013-2015 (at least 3 years follow-up)	1161	1	0.861 (0.09, 4.8)	7	6.03 (2.7, 12.0)	-	-
2013-2014 (at least 4 years follow-up)	659	1	1.52 (0.15, 8.2)	3	4.55 (1.3, 12.6)	-	-

Table S11 Invasive cancer rates at 1 year, 3 years and 6 years post atypia diagnosis per 1000 women estimated from CIF for 3 time periods excluding women with FEA

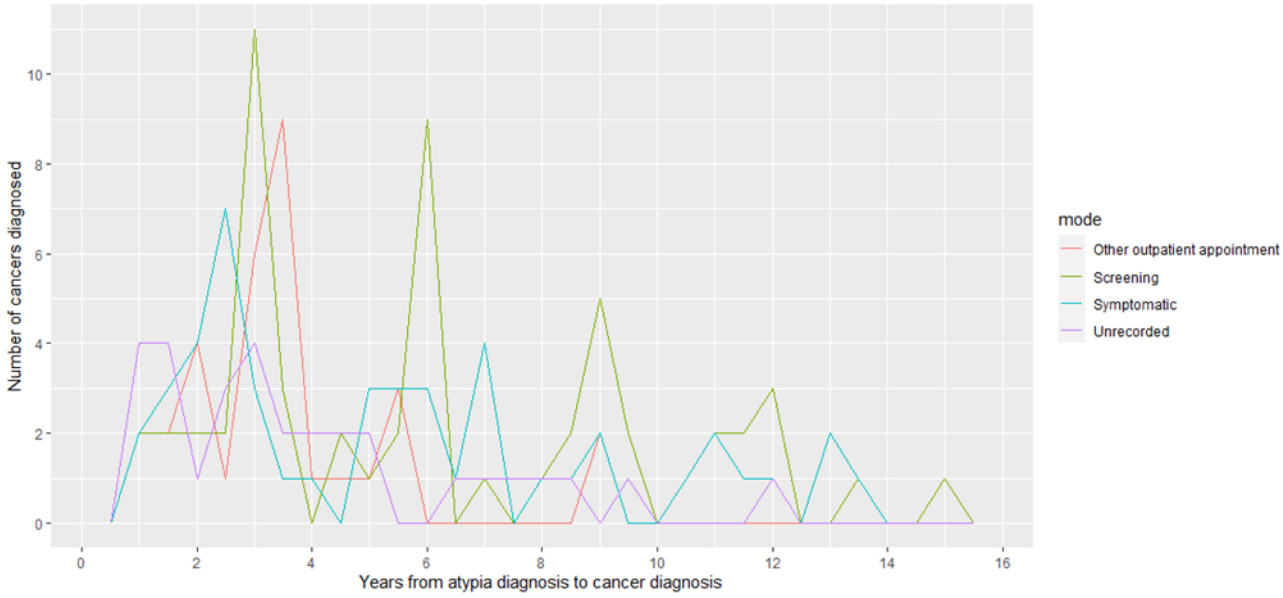
Calendar year at atypia diagnosis	N atypia cases	1 year		3 years		6 years	
		Cancer cases	Cancers per 1000 women (95% CI)	Cancer cases	Cancers per 1000 women (95% CI)	Cancer cases	Cancers per 1000 women (95% CI)
2003-2007	520	0	0	13	25.0 (14.0, 41.1)	33	63.5 (44.7, 86.6)
2008-2012	640	2	3.1 (0.65, 10.7)	17	26.6 (16.1, 41.2)	39	60.9 (44.2, 81.3)
2013-2018	1675	1	0.62 (0.066, 3.47)	7	4.75 (2.1, 9.50)	-	-

Table S12 Invasive cancer rates at 1 year, 3 years and 6 years post atypia diagnosis per 1000 women estimated from CIF for 3 time periods for consecutive cases only

Calendar year at atypia diagnosis	N atypia cases	1 year		3 years		6 years	
		Cancer cases	Cancers per 1000 women (95% CI)	Cancer cases	Cancers per 1000 women (95% CI)	Cancer cases	Cancers per 1000 women (95% CI)
2003-2007	172	0	0	5	29.1 (10.9, 62.6)	15	87.2 (51.1, 135.2
2008-2012	215	2	9.3 (1.87, 30.7)	6	27.9 (11.5, 56.6)	12	55.8 (30.5, 92.1)
2013-2018	1281	1	0.79 (0.083, 4.36)	3	2.5 (0.72, 7.03)	-	-

2.6 Mode of detection of subsequent cancers

Figure S5 Number of cancers (invasive and DCIS) over time since atypia diagnosis by mode of detection



3. Modelling

3.1 Modelling of cancer rates using the cause specific hazard method

Main analysis

Table S13 Model selection for models with invasive cancer and death as causes of outcome.

Number of parameters (p), sample size (n), model log likelihood (Loglik), Akaike's Information criterion (AIC), Bayesian Information Criterion (BIC). Age at atypia diagnosis included grouped (group), continuous linear (cts), continuous linear and quadratic, and as a cubic polynomial spline (spline). Adding continuous linear age as a time varying covariate (tvc) was also explored. The sample size is 6476 because each person contributes two rows to the dataset, one for each cause.

Model	p	n	Loglik	AIC	BIC
No covariates	8	6476	-970.42	1956.84	2011.05
Age (group)	16	6476	-944.64	1921.28	2029.69
Age (cts)	10	6476	-948.79	1917.57	1985.33
Age (cts, tvc)	16	6476	-945.67	1923.34	2031.75
Age (group), year	20	6476	-928.79	1897.58	2033.09
Age (cts), year	14	6476	-932.77	1893.54	1988.40
Age (cts, tvc), year	20	6476	-929.89	1899.77	2035.29
Type	14	6476	-967.40	1962.81	2057.67
Type, age (group)	24	6476	-941.83	1931.67	2094.29
Type, age (cts)	16	6476	-945.80	1923.61	2032.02
Type, age (cts, tvc)	22	6476	-942.71	1929.43	2078.50
Type, age (group), year	26	6476	-926.37	1904.74	2080.91
Type, age (cts), year	20	6476	-930.23	1900.46	2035.98
Type, age (cts, tvc), year	26	6476	-927.30	1906.60	2082.77
Age (group), year, management	24	6476	-927.82	1903.64	2066.26
Age (cts), year, management	18	6476	-931.82	1899.64	2021.60
Type, age (group), year, management	30	6476	-925.12	1910.24	2113.52
Type, age (cts), year, management	24	6476	-929.02	1906.05	2068.67
Age (group), year, calcification	24	6476	-927.63	1903.26	2065.88
Age (cts), year, calcification	18	6476	-931.60	1899.20	2021.17
Type, age (group), year, calcification	30	6476	-925.23	1910.46	2113.74
Type, age (cts), year, calcification	24	6476	-929.10	1906.20	2068.82
Age (spline)	14	6476	-945.80	1919.60	2014.46
Age (spline), year	18	6476	-930.17	1896.34	2018.31
Age (cts, linear, quadratic)	12	6476	-947.12	1918.24	1999.55
Age (cts, linear, quadratic), year	16	6476	-931.52	1895.03	2003.45
Age (cts), year, density	**18**	**6476**	**-927.37**	**1890.73**	**2012.70**
Age (cts), year, density, completeness	20	6476	-926.64	1893.27	2028.79

The AIC statistic show that the best model has age at diagnosis (as a continuous, linear variable), year of diagnosis and background parenchymal breast density as explanatory variables, whereas the BIC suggest that age at diagnosis alone (without year of diagnosis or background parenchymal

density) is the best model. We chose to use the age, year and background parenchymal density model since it is the best according to AIC, the descriptive statistics show that year of diagnosis was important, and clinical opinion that background parenchymal density is important. Adding type of atypia, management, and calcification to the age and year model did not improve the model fit statistics. Adding a variable of consecutive versus non-consecutive cases did not improve the model fit. Including age as a continuous, linear term was the best method, having better model fit statistics than the equivalent models for group, linear and quadratic and spline, showing the extra complexity to be unnecessary.

Table S14 Cancer rates (fitted values) at 1, 3, and 6 years since atypia diagnosis from main model (by age, year of diagnosis and background parenchymal breast density). Cumulative incidence of invasive cancer per 1000 women

Year of atypia diagnosis	Age	1 year		3 years		6 years	
		Est	95% CI	Est	95% CI	Est	95% CI
High density							
2003 to 2007	50	1.86	(0.14,3.59)	32.31	(18.75,45.86)	70.28	(44.75,95.8)
2003 to 2007	55	2.05	(0.17,3.93)	35.48	(21.41,49.54)	76.98	(51.05,102.9)
2003 to 2007	60	2.26	(0.18,4.33)	38.95	(23.14,54.76)	84.24	(55.01,113.46)
2003 to 2007	65	2.48	(0.15,4.81)	42.73	(23.69,61.77)	92.07	(56.18,127.97)
2003 to 2007	70	2.73	(0.08,5.38)	46.85	(23.05,70.66)	100.47	(54.7,146.25)
2008 to 2012	50	1.45	(0.12,2.77)	25.14	(14.6,35.68)	54.91	(35.25,74.56)
2008 to 2012	55	1.59	(0.14,3.04)	27.61	(16.44,38.79)	60.17	(39.65,80.68)
2008 to 2012	60	1.75	(0.14,3.36)	30.32	(17.51,43.12)	65.87	(42.12,89.61)
2008 to 2012	65	1.92	(0.11,3.74)	33.27	(17.69,48.85)	72	(42.4,101.61)
2008 to 2012	70	2.12	(0.05,4.19)	36.48	(16.95,56.01)	78.56	(40.66,116.45)
2013 to 2018	50	0.49	(0.02,0.96)	8.55	(4.13,12.97)	18.83	(9,28.67)
2013 to 2018	55	0.54	(0.03,1.05)	9.39	(4.63,14.15)	20.65	(10.09,31.21)
2013 to 2018	60	0.59	(0.02,1.16)	10.31	(4.93,15.7)	22.6	(10.7,34.5)
2013 to 2018	65	0.65	(0.01,1.29)	11.32	(4.95,17.68)	24.69	(10.73,38.64)
2013 to 2018	70	0.71	(0,1.44)*	12.4	(4.69,20.11)	26.87	(10.13,43.62)
Low density							
2003 to 2007	50	1.42	(0.09,2.74)	24.63	(13.85,35.41)	53.83	(33.19,74.48)
2003 to 2007	55	1.56	(0.13,2.99)	27.06	(16.32,37.8)	59.01	(39.1,78.92)
2003 to 2007	60	1.71	(0.15,3.28)	29.72	(18.2,41.23)	64.63	(43.53,85.72)
2003 to 2007	65	1.89	(0.15,3.62)	32.62	(19.19,46.04)	70.69	(45.71,95.67)
2003 to 2007	70	2.07	(0.11,4.04)	35.78	(19.19,52.37)	77.2	(45.54,108.86)
2008 to 2012	50	1.1	(0.09,2.11)	19.15	(10.99,27.31)	41.98	(26.63,57.32)
2008 to 2012	55	1.21	(0.11,2.3)	21.04	(12.78,29.3)	46.02	(30.97,61.07)
2008 to 2012	60	1.33	(0.13,2.53)	23.11	(14.04,32.17)	50.4	(33.96,66.85)
2008 to 2012	65	1.46	(0.12,2.81)	25.36	(14.59,36.13)	55.13	(35.11,75.14)
2008 to 2012	70	1.61	(0.08,3.13)	27.82	(14.38,41.25)	60.17	(34.45,85.88)
2013 to 2018	50	0.37	(0.02,0.73)	6.5	(3.14,9.85)	14.33	(6.85,21.8)
2013 to 2018	55	0.41	(0.02,0.79)	7.14	(3.64,10.64)	15.71	(7.92,23.5)
2013 to 2018	60	0.45	(0.02,0.87)	7.84	(3.99,11.69)	17.19	(8.66,25.73)

2013 to 2018	65	0.49	(0.02,0.97)	8.6	(4.13,13.07)	18.77	(8.95,28.6)
2013 to 2018	70	0.54	(0.01,1.08)	9.42	(4.05,14.79)	20.42	(8.72,32.12)
Unrecorded density							
2003 to 2007	50	1.84	(0,4.03)*	31.78	(4.64,58.92)	68.95	(12.78,125.13)
2003 to 2007	55	2.02	(0,4.41)*	34.87	(5.69,64.04)	75.35	(15.38,135.32)
2003 to 2007	60	2.22	(0,4.85)*	38.22	(6.3,70.14)	82.15	(17.02,147.29)
2003 to 2007	65	2.44	(0,5.36)*	41.84	(6.31,77.38)	89.29	(17.38,161.2)
2003 to 2007	70	2.69	(0,5.95)*	45.73	(5.58,85.87)	96.61	(16.2,177.02)
2008 to 2012	50	1.42	(0,3.14)*	24.71	(2.99,46.44)	53.78	(8.55,99)
2008 to 2012	55	1.57	(0,3.44)*	27.11	(3.62,50.6)	58.74	(10.15,107.32)
2008 to 2012	60	1.72	(0,3.79)*	29.71	(3.88,55.53)	63.98	(10.96,117)
2008 to 2012	65	1.89	(0,4.19)*	32.5	(3.67,61.33)	69.41	(10.73,128.1)
2008 to 2012	70	2.08	(0,4.66)*	35.48	(2.88,68.07)	74.86	(9.24,140.48)
2013 to 2018	50	0.48	(0,1.07)*	8.38	(0.62,16.15)	18.33	(1.36,35.3)
2013 to 2018	55	0.53	(0,1.17)*	9.19	(0.77,17.6)	19.96	(1.7,38.23)
2013 to 2018	60	0.58	(0,1.29)*	10.05	(0.81,19.29)	21.64	(1.77,41.52)
2013 to 2018	65	0.64	(0,1.43)*	10.96	(0.68,21.25)	23.29	(1.48,45.1)
2013 to 2018	70	0.7	(0,1.59)*	11.9	(0.35,23.46)	24.79	(0.77,48.8)

***The assumptions used to calculate the confidence intervals can occasionally lead to the lower bound taking a small negative value. These are given as zero in the table.**

The CIF for the causes in the main model (invasive cancer and death) are evaluated at 1, 3 and 6 years in table S14. For someone aged 60 with high background parenchymal density the estimated rate of invasive cancer at 3 years for those diagnosed with atypia between 2003 and 2007 was 38.95 per 1000 women, 95% CI (23.14,49.54), and for those diagnosed with atypia between 2013 and 2018 was 10.31 per 1000 women, 95% CI (4.93,15.70). For low background parenchymal density, the corresponding rates were 29.72, (18.20,41.23), and 7.84, (3.99,11.69).

Table S15 Comparison of the risk of subsequent invasive cancers considering different factors

Comparison	**Hazard ratio**	**95% CI**	**p**
Main model			
Age*	1.019	0.996, 1.043	0.110
Low background parenchymal breast density vs high	0.760	0.537, 1.075	0.120
Years 2008 to 2013 vs years 2003 to 2007	0.775	0.525, 1.145	0.201
Years 2013 to 2018 vs years 2003 to 2007	0.262	0.149, 0.461	<0.001
Individual models with variables added to main model in turn			
Variable: Atypia type			
FEA vs ADH	1.167	0.546, 2.494	0.690
LISN vs ADH	1.137	0.777, 1.663	0.509
Mixed vs ADH	1.712	1.054, 2.782	0.030
Variable: Management			
Single diagnostic needle biopsy vs Second line vacuum assisted biopsy/excision	0.771	0.368, 1.618	0.492
Single diagnostic needle biopsy vs Surgery	0.750	0.451, 1.246	0.267

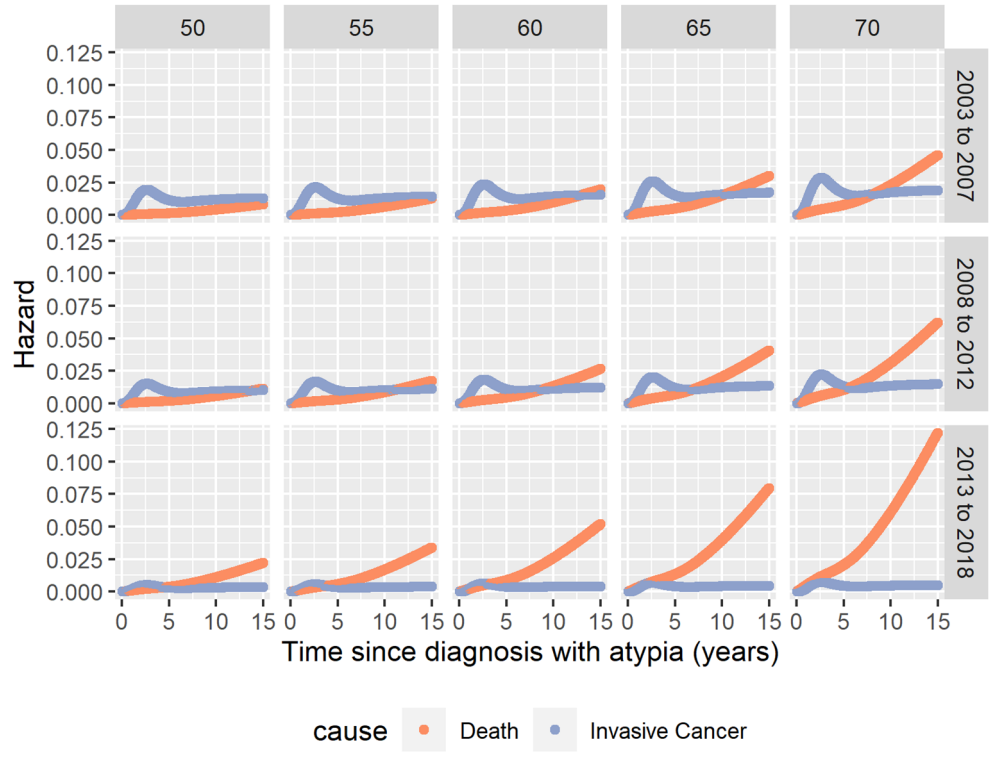
Surgery vs Second line vacuum assisted biopsy/excision	1.029	0.543, 1.948	0.930
Variable: consecutive cases			
Non-consecutive vs consecutive cases	1.010	0.705, 1.447	0.957

*Age is a continuous variable measured in years, so the change is over a period of one year

The hazard ratios presented in Table S15 come from different models. Age, density and year of diagnosis was compared in the main model. Other variables were added in turn to the main model to derive hazard ratios for the relevant comparisons.

Figure S6 Cause-specific hazard function for each cause of outcome from the main model by time since atypia diagnosis. Shown by age at diagnosis, year of diagnosis and background parenchymal density (high in figure a and low in figure b)

a
High density



b
Low density

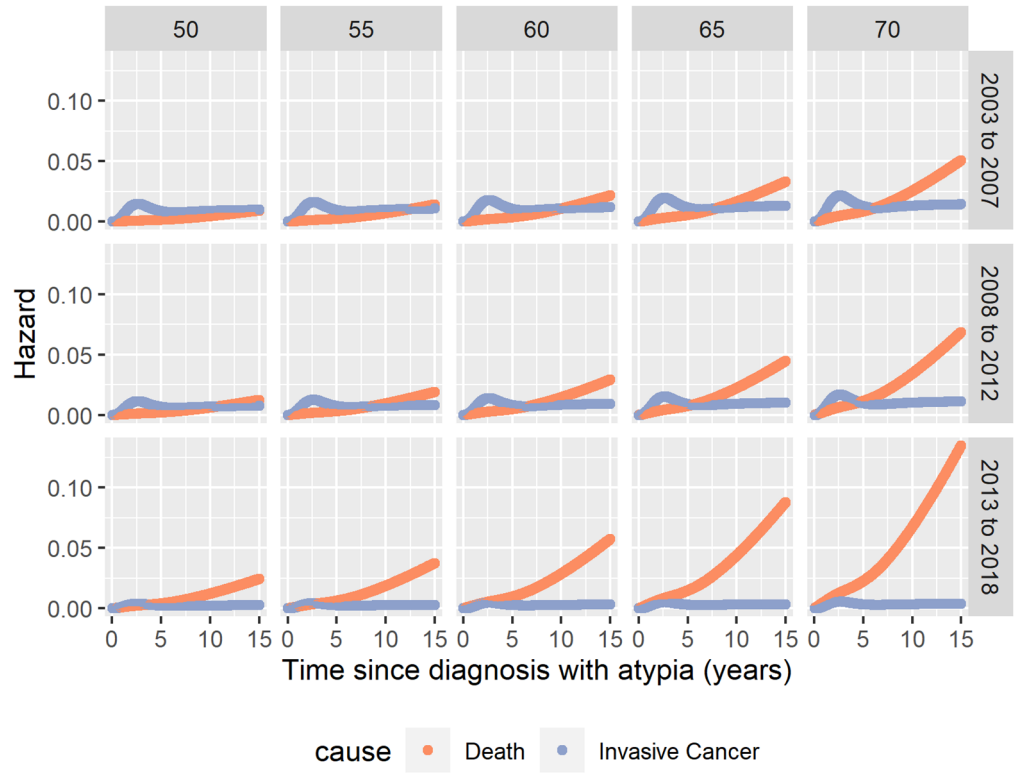
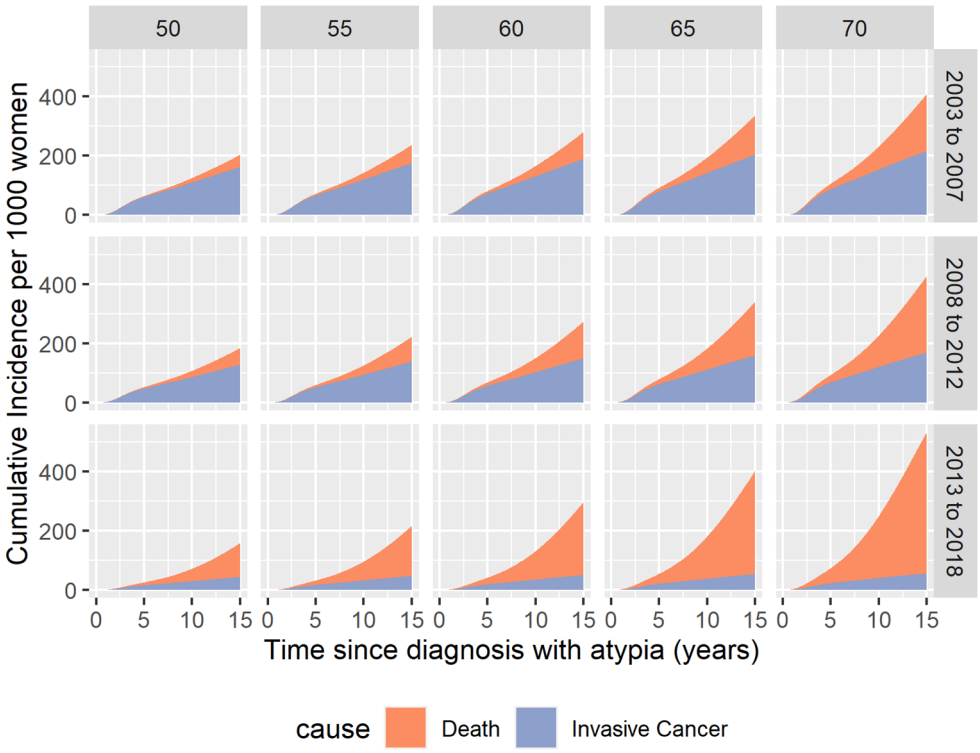
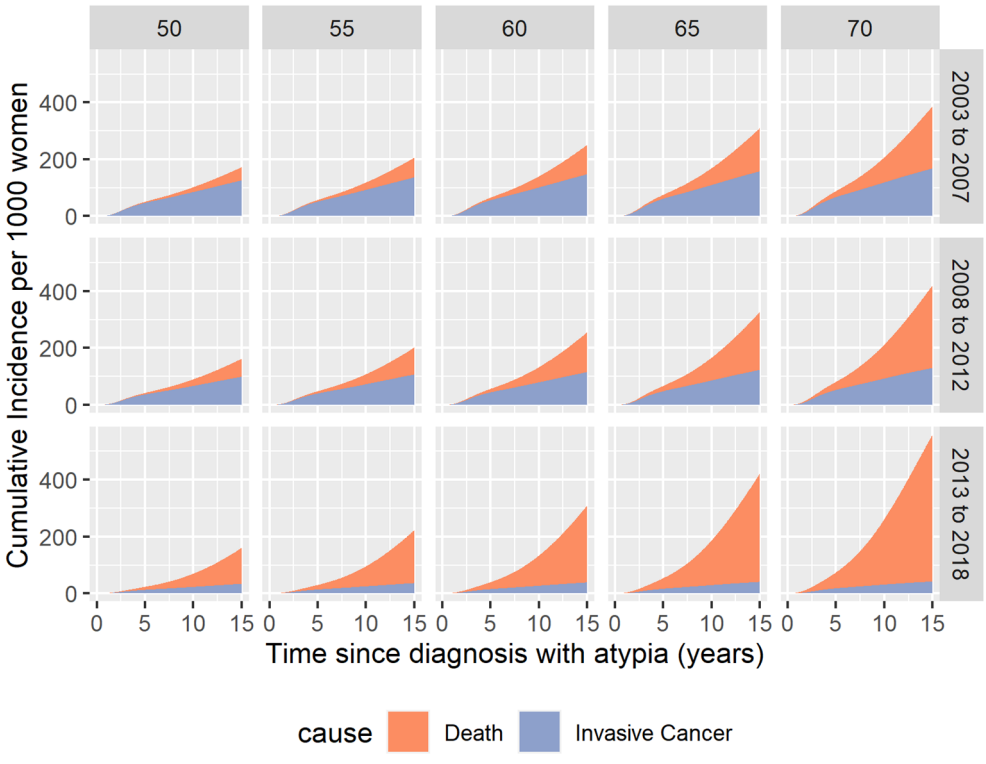


Figure S7 Stacked cumulative incidence plots from the main model. Show cumulative incidence of death and invasive cancer since diagnosis with atypia for people aged 50, 55, 60, 65, and 70 at time of diagnosis and diagnosed in the three periods: 2003 to 2007, 2008 to 2012, and 2013 to 2018; with high background parenchymal density shown in figure a and low background parenchymal density in figure b

a
High density



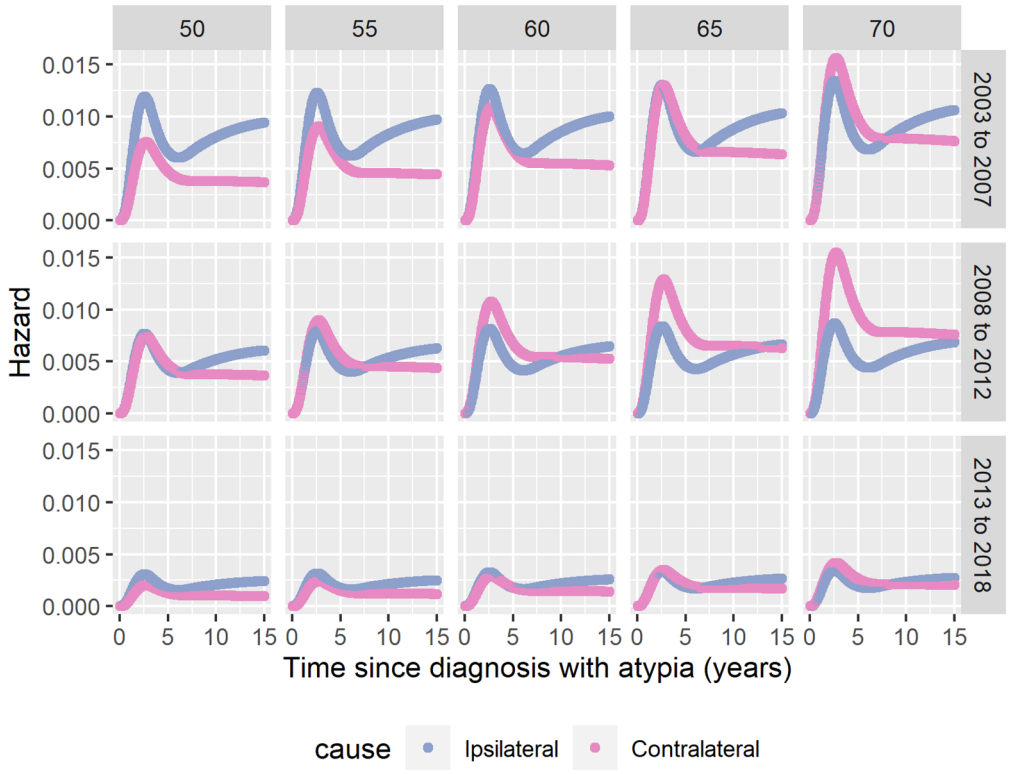
b
Low density



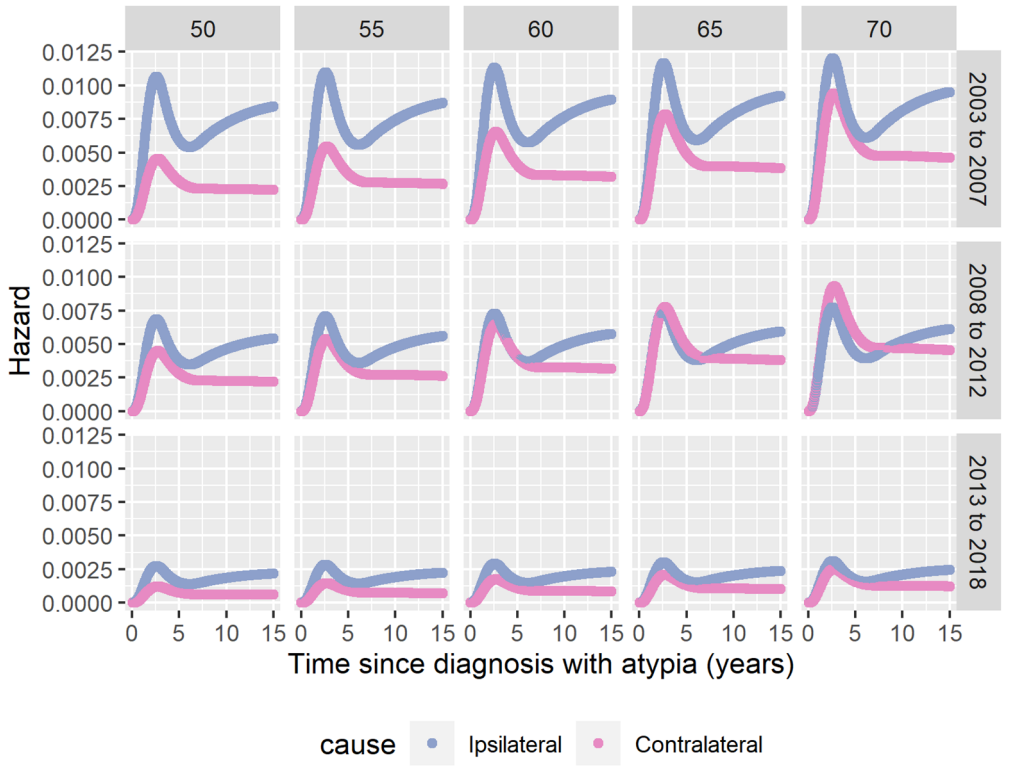
Results for invasive cancer split into ipsilateral and contralateral cancers

Figure S8 Cause-specific hazards (a, b), stacked cumulative incidence functions (c, d) and cumulative incidence functions (e, f) evaluated at 1 year, 3 years, and 6 years since diagnosis with atypia, from the main model with death and invasive cancer split into ipsilateral and contralateral. Only ipsilateral and contralateral cancers are shown.

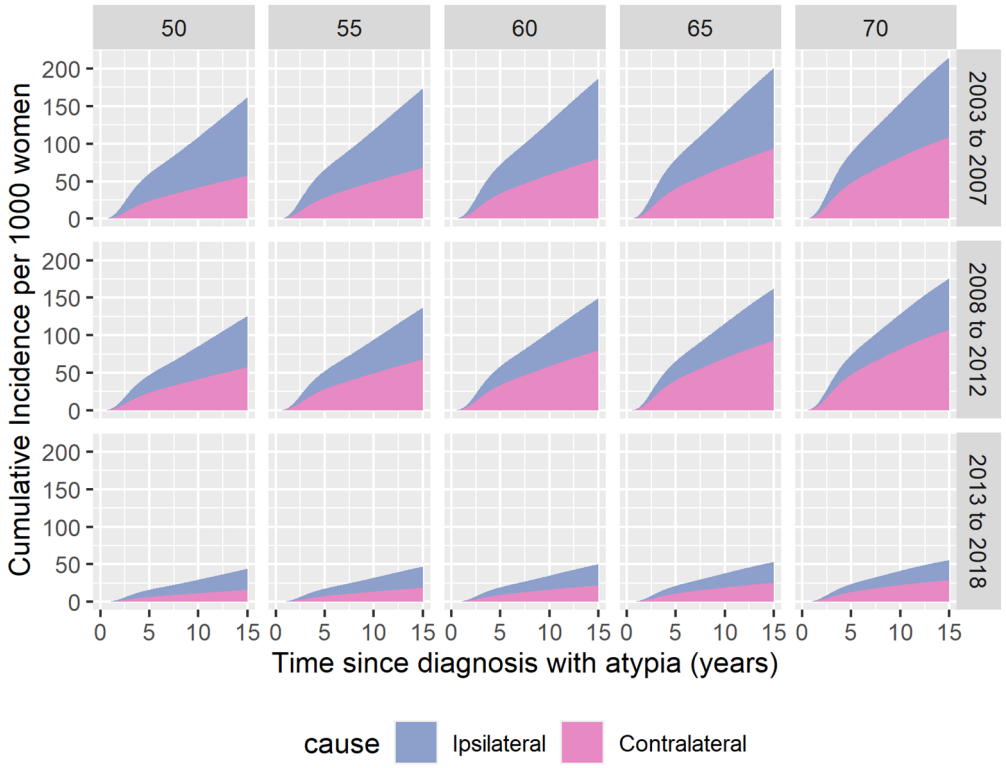
a
High density



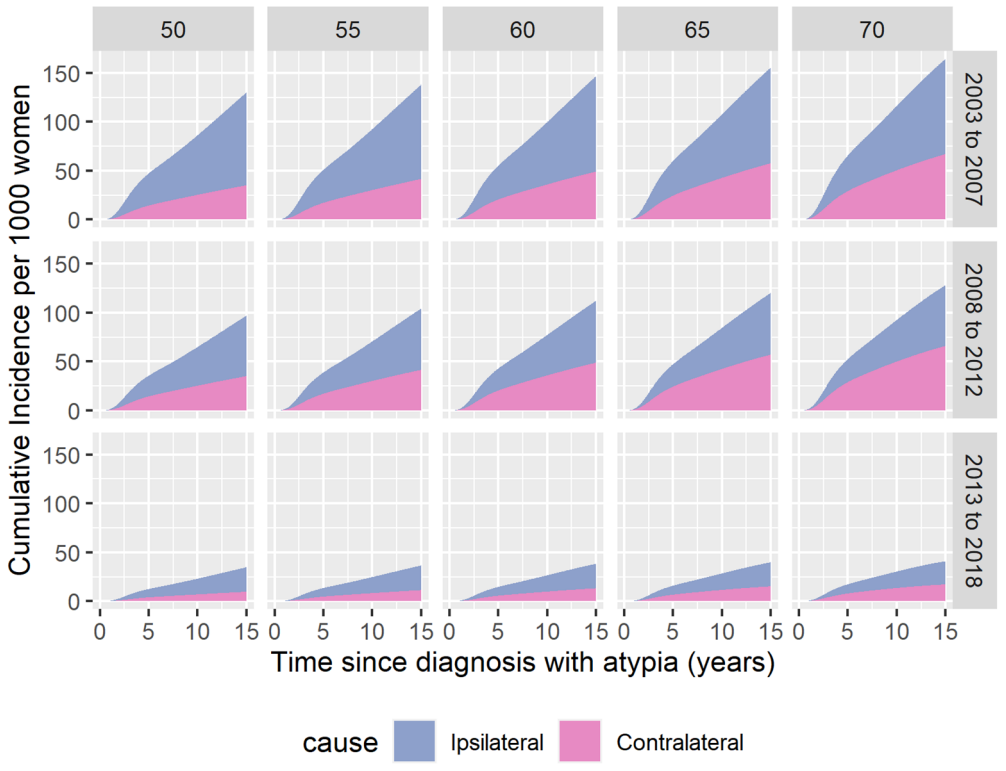
b
Low density

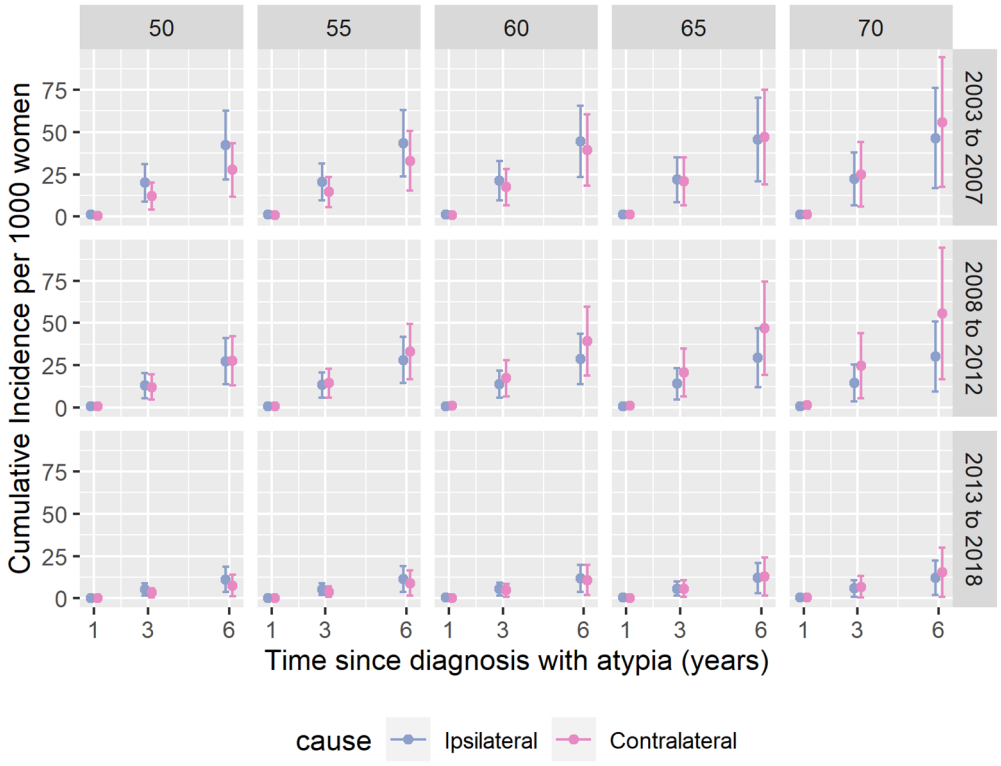
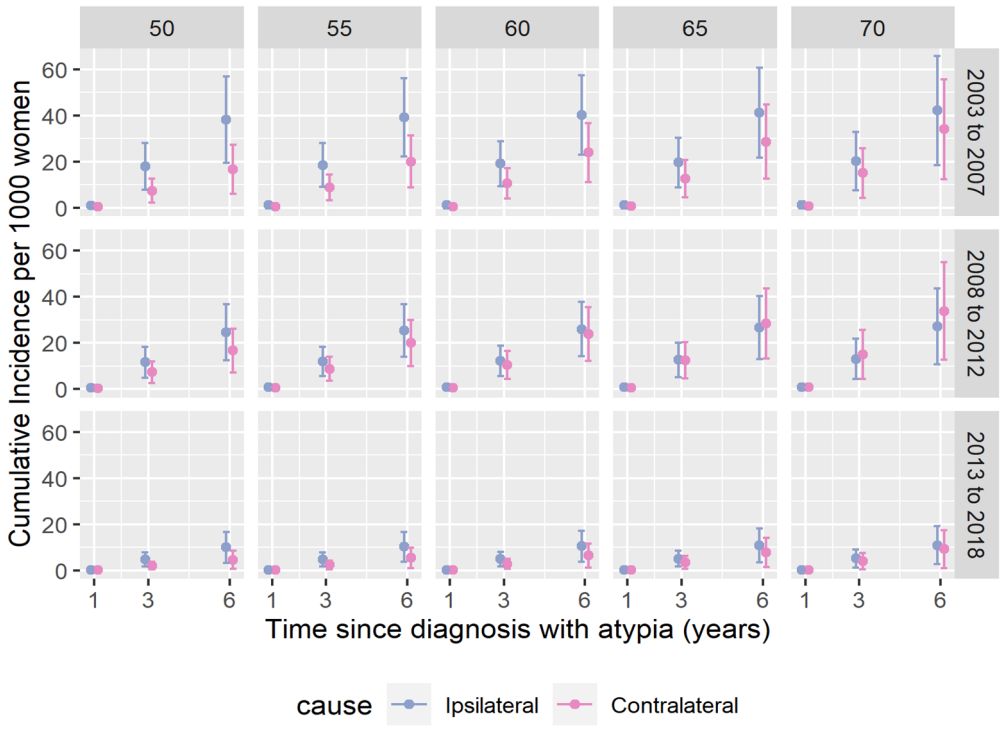


c
High
density



d
Low
density



e High density	
f Low density	

Model when the outcome is the earlier of invasive cancer or DCIS

Table S16 Fitted values at 1, 3, and 6 years since atypia diagnosis from main model with invasive cancer and DCIS combined. Cumulative incidence of outcome cause per 1000 women.

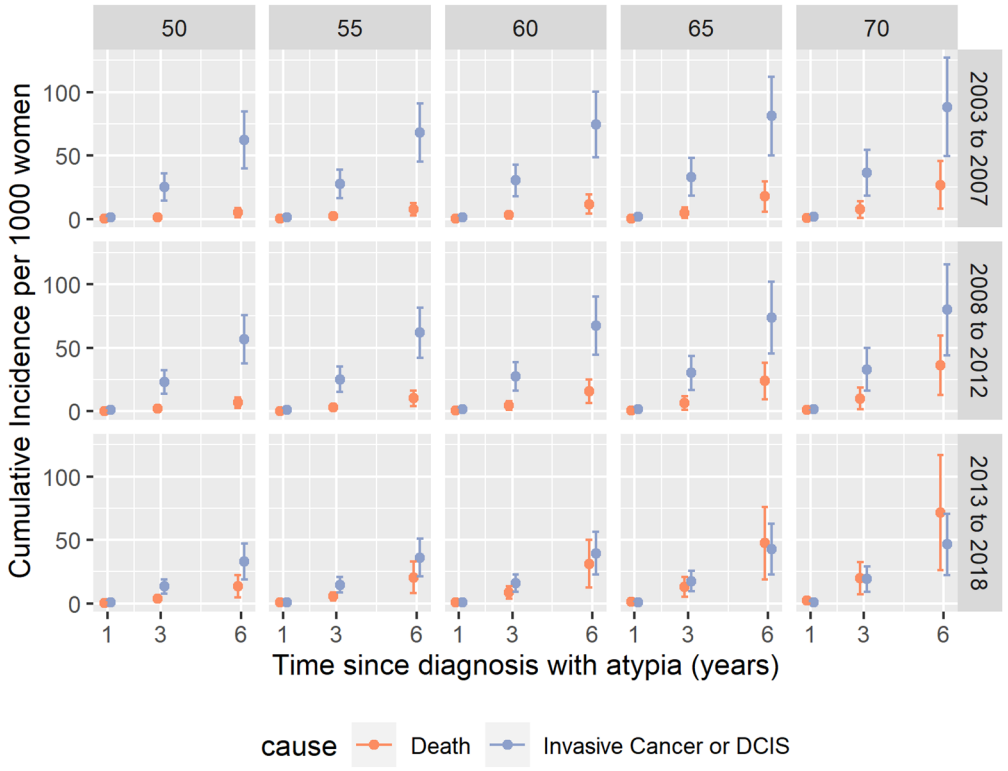
		1 year		3 years		6 years	
Year	Age	Est.	95% CI	Est.	95% CI	Est.	95% CI
High density							
2003 to 2007	50	1.21	(0.07,2.36)	25.3	(14.58,36.02)	62.34	(39.94,84.75)
2003 to 2007	55	1.33	(0.09,2.58)	27.72	(16.49,38.95)	68.12	(45.12,91.13)
2003 to 2007	60	1.46	(0.09,2.83)	30.36	(17.81,42.91)	74.37	(48.59,100.15)
2003 to 2007	65	1.6	(0.07,3.13)	33.23	(18.38,48.08)	81.1	(50,112.2)
2003 to 2007	70	1.76	(0.03,3.48)	36.35	(18.17,54.53)	88.28	(49.37,127.19)
2008 to 2012	50	1.1	(0.08,2.12)	22.92	(13.54,32.3)	56.55	(37.48,75.63)
2008 to 2012	55	1.2	(0.09,2.32)	25.11	(15.14,35.08)	61.79	(41.86,81.72)
2008 to 2012	60	1.32	(0.09,2.55)	27.5	(16.16,38.83)	67.44	(44.51,90.37)
2008 to 2012	65	1.45	(0.07,2.82)	30.09	(16.5,43.69)	73.5	(45.22,101.78)
2008 to 2012	70	1.59	(0.03,3.15)	32.91	(16.12,49.7)	79.93	(44.1,115.77)
2013 to 2018	50	0.64	(0.04,1.23)	13.34	(7.75,18.92)	33.09	(19.08,47.1)
2013 to 2018	55	0.7	(0.05,1.35)	14.61	(8.65,20.58)	36.15	(21.23,51.06)
2013 to 2018	60	0.77	(0.05,1.48)	15.99	(9.2,22.79)	39.42	(22.54,56.29)
2013 to 2018	65	0.84	(0.04,1.64)	17.49	(9.36,25.63)	42.88	(22.87,62.88)
2013 to 2018	70	0.92	(0.02,1.83)	19.11	(9.09,29.12)	46.46	(22.16,70.77)
Low density							
2003 to 2007	50	0.95	(0.05,1.84)	19.77	(11.12,28.41)	48.9	(30.57,67.23)
2003 to 2007	55	1.04	(0.07,2.01)	21.66	(12.92,30.4)	53.46	(35.5,71.42)
2003 to 2007	60	1.14	(0.08,2.2)	23.72	(14.33,33.12)	58.4	(39.3,77.49)
2003 to 2007	65	1.25	(0.08,2.42)	25.97	(15.16,36.79)	63.71	(41.43,85.99)
2003 to 2007	70	1.37	(0.06,2.68)	28.42	(15.35,41.49)	69.39	(41.74,97.03)
2008 to 2012	50	0.86	(0.06,1.65)	17.9	(10.49,25.31)	44.32	(29.14,59.5)
2008 to 2012	55	0.94	(0.08,1.8)	19.61	(12.06,27.17)	48.45	(33.51,63.38)
2008 to 2012	60	1.03	(0.08,1.97)	21.48	(13.22,29.74)	52.9	(36.64,69.16)
2008 to 2012	65	1.13	(0.08,2.18)	23.51	(13.82,33.2)	57.68	(38.08,77.27)
2008 to 2012	70	1.24	(0.06,2.42)	25.72	(13.82,37.61)	62.74	(37.84,87.64)
2013 to 2018	50	0.5	(0.03,0.96)	10.4	(6.07,14.74)	25.86	(14.96,36.76)
2013 to 2018	55	0.54	(0.04,1.04)	11.4	(6.95,15.84)	28.25	(17.09,39.4)
2013 to 2018	60	0.6	(0.05,1.14)	12.48	(7.6,17.35)	30.8	(18.62,42.98)
2013 to 2018	65	0.65	(0.05,1.26)	13.64	(7.92,19.37)	33.49	(19.33,47.66)
2013 to 2018	70	0.72	(0.03,1.4)	14.9	(7.88,21.92)	36.27	(19.15,53.4)
Unrecorded density							
2003 to 2007	50	1.39	(0,2.99)*	28.95	(6.78,51.13)	70.91	(19.88,121.93)
2003 to 2007	55	1.53	(0,3.26)*	31.68	(7.92,55.45)	77.24	(23,131.48)
2003 to 2007	60	1.68	(0,3.58)*	34.64	(8.7,60.58)	83.94	(25.21,142.67)
2003 to 2007	65	1.84	(0,3.94)*	37.82	(9,66.65)	90.92	(26.22,155.63)
2003 to 2007	70	2.02	(0,4.36)*	41.22	(8.7,73.75)	98	(25.74,170.25)
2008 to 2012	50	1.26	(0,2.71)*	26.22	(5.74,46.69)	64.24	(17.1,111.38)

2008 to 2012	55	1.38	(0,2.96)*	28.68	(6.62,50.74)	69.91	(19.53,120.28)
2008 to 2012	60	1.52	(0,3.25)*	31.34	(7.16,55.51)	75.85	(21.1,130.61)
2008 to 2012	65	1.66	(0,3.58)*	34.18	(7.24,61.12)	81.95	(21.51,142.38)
2008 to 2012	70	1.82	(0,3.97)*	37.2	(6.78,67.62)	87.96	(20.54,155.39)
2013 to 2018	50	0.73	(0,1.57)*	15.23	(3.34,27.12)	37.41	(8.36,66.46)
2013 to 2018	55	0.8	(0,1.71)*	16.64	(3.83,29.45)	40.57	(9.53,71.61)
2013 to 2018	60	0.88	(0,1.88)*	18.14	(4.1,32.18)	43.76	(10.15,77.36)
2013 to 2018	65	0.96	(0,2.07)*	19.72	(4.11,35.33)	46.82	(10.07,83.57)
2013 to 2018	70	1.05	(0,2.29)*	21.34	(3.78,38.9)	49.5	(9.11,89.9)

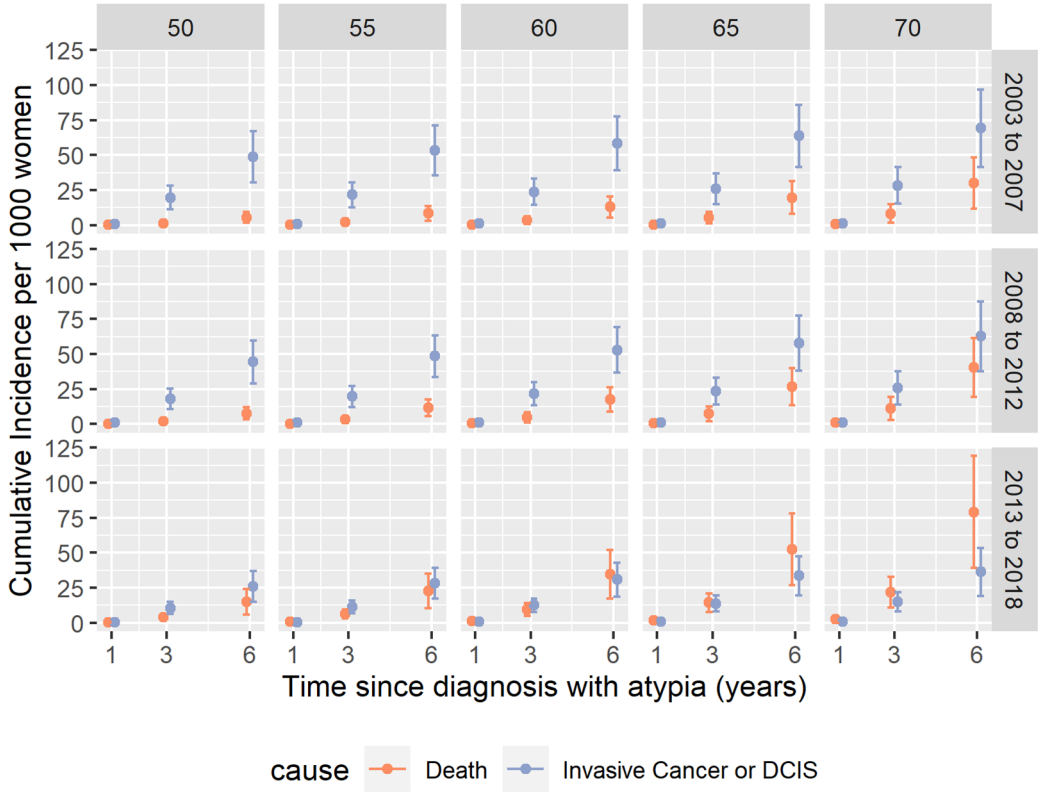
*The assumptions used to calculate the confidence intervals can occasionally lead to the lower bound taking a small negative value. These are given as zero in the table

Figure S9 Cumulative incidence functions evaluated at 1 year, 3 years, and 6 years since diagnosis with atypia, from the main model with invasive cancer or DCIS combined for high (a) and low (b) background parenchymal density

a
High density



b
Low density



3.2 Modelling of cancer rates using the subdistribution method

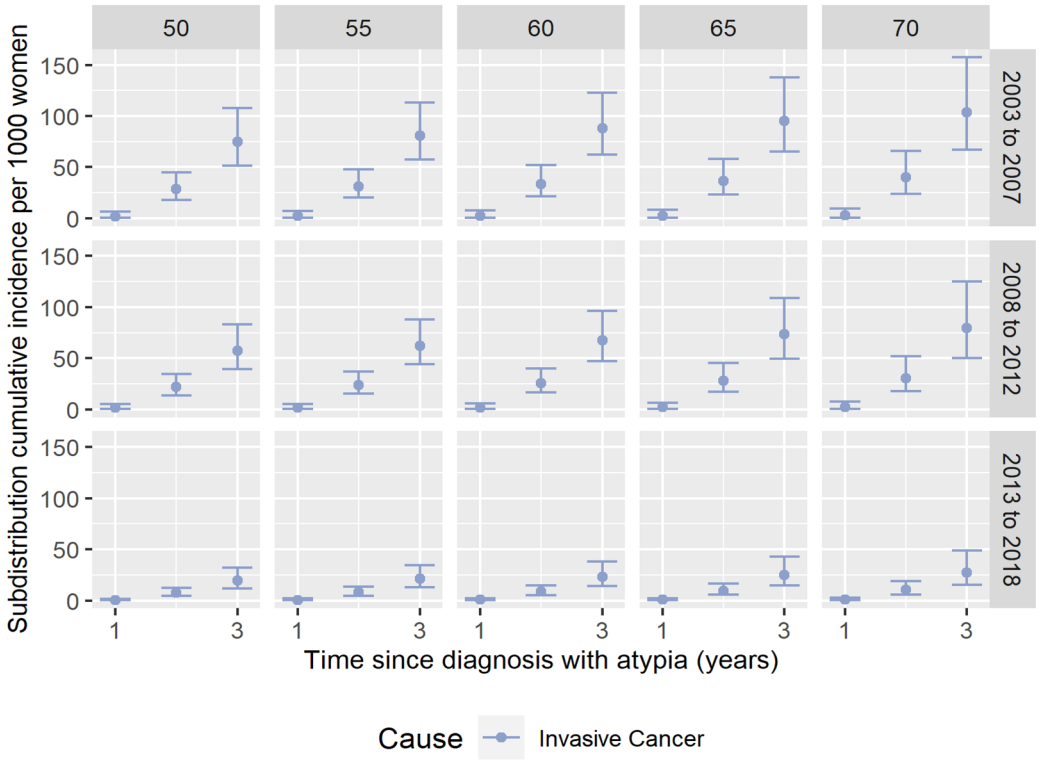
Table S17 Cancer rates (fitted values) at 1, 3, and 6 years since atypia diagnosis from main model, using the subdistribution method. Cumulative incidence of invasive cancer per 1000 women

		1 year		3 years		6 years	
Year	Age	Est	95% CI	Est	95% CI	Est	95% CI
Invasive cancer, high density							
2003 to 2007	50	2.03	(0.62,6.62)	28.47	(18,44.88)	74.65	(51.55,107.51)
2003 to 2007	55	2.21	(0.68,7.14)	30.96	(20.08,47.6)	81.02	(57.68,113.21)
2003 to 2007	60	2.4	(0.74,7.78)	33.67	(21.81,51.82)	87.9	(62.46,123)
2003 to 2007	65	2.62	(0.8,8.56)	36.61	(23.05,57.91)	95.34	(65.53,137.68)
2003 to 2007	70	2.85	(0.85,9.52)	39.81	(23.84,66.1)	103.37	(67.09,157.52)
2008 to 2012	50	1.55	(0.47,5.05)	21.76	(13.73,34.39)	57.38	(39.56,82.86)
2008 to 2012	55	1.68	(0.52,5.46)	23.67	(15.22,36.72)	62.32	(43.95,88.01)
2008 to 2012	60	1.83	(0.56,5.96)	25.75	(16.42,40.26)	67.67	(47.25,96.47)
2008 to 2012	65	1.99	(0.6,6.58)	28.01	(17.28,45.25)	73.47	(49.3,108.79)
2008 to 2012	70	2.17	(0.64,7.33)	30.46	(17.8,51.89)	79.74	(50.31,125.2)
2013 to 2018	50	0.52	(0.15,1.71)	7.3	(4.33,12.29)	19.5	(11.78,32.19)
2013 to 2018	55	0.56	(0.17,1.85)	7.95	(4.78,13.2)	21.21	(12.99,34.54)
2013 to 2018	60	0.61	(0.18,2.03)	8.66	(5.15,14.52)	23.08	(13.99,37.97)
2013 to 2018	65	0.67	(0.2,2.24)	9.42	(5.43,16.32)	25.11	(14.72,42.68)
2013 to 2018	70	0.72	(0.21,2.5)	10.26	(5.62,18.69)	27.31	(15.19,48.85)
Invasive cancer, low density							
2003 to 2007	50	1.54	(0.48,5)	21.75	(14.04,33.62)	57.35	(40.29,81.33)
2003 to 2007	55	1.68	(0.52,5.38)	23.66	(15.75,35.47)	62.29	(45.43,85.13)
2003 to 2007	60	1.83	(0.57,5.86)	25.74	(17.17,38.49)	67.64	(49.46,92.17)
2003 to 2007	65	1.99	(0.62,6.44)	28	(18.19,42.97)	73.44	(51.99,103.24)
2003 to 2007	70	2.17	(0.66,7.15)	30.45	(18.81,49.1)	79.7	(53.2,118.56)
2008 to 2012	50	1.18	(0.36,3.81)	16.61	(10.73,25.65)	43.98	(30.99,62.25)
2008 to 2012	55	1.28	(0.4,4.11)	18.07	(11.96,27.26)	47.8	(34.67,65.73)
2008 to 2012	60	1.39	(0.43,4.48)	19.66	(12.95,29.8)	51.94	(37.44,71.85)
2008 to 2012	65	1.52	(0.47,4.94)	21.39	(13.64,33.47)	56.43	(39.1,81.12)
2008 to 2012	70	1.65	(0.5,5.5)	23.28	(14.05,38.43)	61.3	(39.86,93.69)
2013 to 2018	50	0.39	(0.12,1.32)	5.56	(3.22,9.59)	14.88	(8.73,25.3)
2013 to 2018	55	0.43	(0.13,1.42)	6.06	(3.57,10.28)	16.19	(9.65,27.09)
2013 to 2018	60	0.47	(0.14,1.55)	6.6	(3.86,11.26)	17.62	(10.43,29.68)
2013 to 2018	65	0.51	(0.15,1.71)	7.18	(4.08,12.62)	19.17	(11.03,33.23)
2013 to 2018	70	0.55	(0.16,1.91)	7.82	(4.24,14.4)	20.86	(11.43,37.9)
Invasive cancer, unrecorded density							
2003 to 2007	50	1.93	(0.47,7.93)	27.1	(11.1,65.4)	71.15	(30.78,159.9)
2003 to 2007	55	2.1	(0.51,8.55)	29.48	(12.25,70.07)	77.22	(33.94,170.59)
2003 to 2007	60	2.29	(0.56,9.31)	32.06	(13.33,76.06)	83.8	(36.91,184.29)
2003 to 2007	65	2.49	(0.61,10.22)	34.86	(14.31,83.62)	90.91	(39.56,201.53)
2003 to 2007	70	2.71	(0.65,11.31)	37.9	(15.17,93.05)	98.58	(41.83,222.83)
2008 to 2012	50	1.47	(0.35,6.08)	20.71	(8.38,50.72)	54.66	(23.3,125.41)

2008 to 2012	55	1.6	(0.39,6.58)	22.53	(9.21,54.55)	59.37	(25.62,134.44)
2008 to 2012	60	1.74	(0.42,7.18)	24.51	(10,59.44)	64.48	(27.77,145.96)
2008 to 2012	65	1.9	(0.46,7.9)	26.66	(10.71,65.6)	70.02	(29.68,160.43)
2008 to 2012	70	2.07	(0.49,8.76)	29	(11.32,73.26)	76	(31.32,178.3)
2013 to 2018	50	0.49	(0.12,2.01)	6.95	(2.81,17.16)	18.56	(7.61,44.9)
2013 to 2018	55	0.53	(0.13,2.18)	7.56	(3.08,18.51)	20.19	(8.35,48.39)
2013 to 2018	60	0.58	(0.14,2.38)	8.23	(3.34,20.23)	21.97	(9.05,52.84)
2013 to 2018	65	0.63	(0.15,2.62)	8.96	(3.57,22.41)	23.9	(9.67,58.45)
2013 to 2018	70	0.69	(0.16,2.91)	9.76	(3.77,25.13)	26	(10.2,65.44)

Figure S10 Cumulative incidence function for invasive cancer from the main model using the subdistribution method, evaluated at 1 year, 3 years, and 6 years since diagnosis with atypia; by age at diagnosis, year of diagnosis and background parenchymal density (high in figure a, low in figure b)

a
High density



b
Low density