# Identification of recurrences in women diagnosed with early invasive breast cancer using routinely collected data in England

# Supplementary Materials

**Derivation of algorithm**



**External validation**

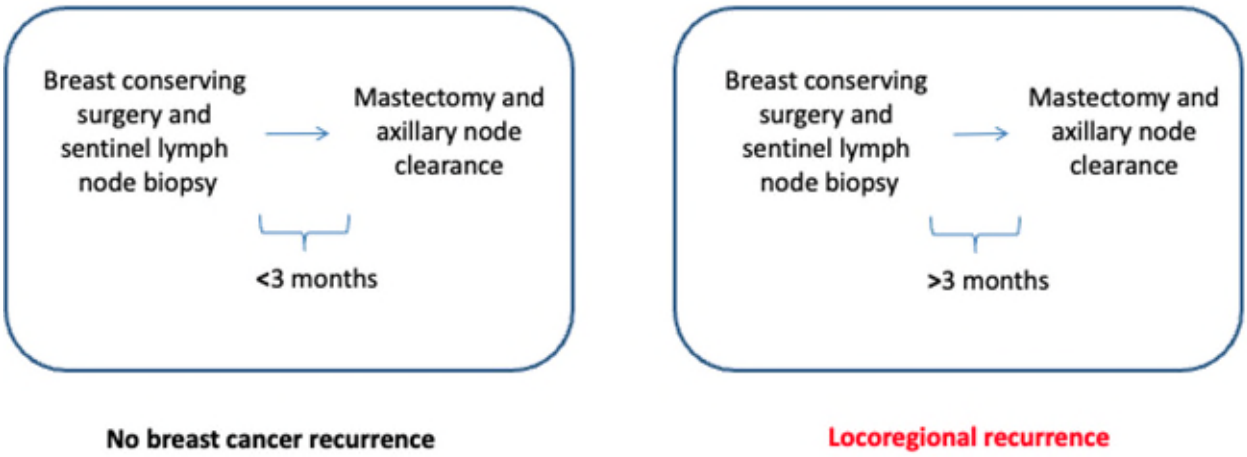
**Table S1. Clinical outcomes recorded in West Midlands Cancer Intelligence Unit (WMCIU) database and outcomes for algorithm based on routinely collected data (RCD).**

| **Outcomes in WMCIU database** listed in order of priority for algorithm development | **Code** | **Outcomes for algorithm based on RCD** |
|---|---|---|
| | | |
| Not eligible for study (e.g. not resident in WMCIU region) | A[a] | - |
| Death certificate registration only or date of diagnosis same as date of death | B2[a] | - |
| Stage 4 disease, metastases or palliative treatment <3 months after diagnosis | B1[a] | - |
| Death from breast cancer with previous breast specific surgery | C01a | Death from breast cancer |
| Death from breast cancer without known breast specific surgery | C01b | |
| Confirmed distant metastases to liver/lung/bone/brain | C03a(i) | Distant recurrence |
| Confirmed distant metastasis to other locations | C03a(ii) | |
| Record of palliative care | C03a(iii) | |
| Unconfirmed distant metastasis to liver/lung/bone/brain | C03b | |
| Contralateral breast cancer | C07 | Contralateral breast cancer |
| Recurrence in ipsilateral regional lymph nodes | C04a | Locoregional recurrence |
| Recurrence in regional lymph nodes with no laterality recorded | C04b | |
| Recurrence in ipsilateral breast | C05 | |
| Recurrence, type unknown | C06 | Recurrence, type unknown |
| Microscopically confirmed primary cancer of liver/lung/brain/bone | C08a | Non-breast cancer malignancy |
| Microscopically unconfirmed primary cancer of liver/lung/brain/bone | C08b | |
| New primary non-breast cancer | C08c | |
| Death from non-breast cancer | C09 | Non-breast-cancer death |
| Death with no cause recorded in the registry with previous breast surgery | C10a | |
| Death with no cause recorded in the registry without previous breast surgery | C10b | |
| Death from cause other than cancer | C11 | |
| Embarkation | D01 | No event recorded |
| No events of any type during study period | E | |

[a] Women with these outcomes were excluded from further consideration during the comparison with routinely collected data.

Where two or more outcomes occurred on the same day, the one listed first in the table took priority

**(a) Initial algorithm rule**




**(b) Algorithm rule refined after examination of data from 150 women from the AZURE cohort**

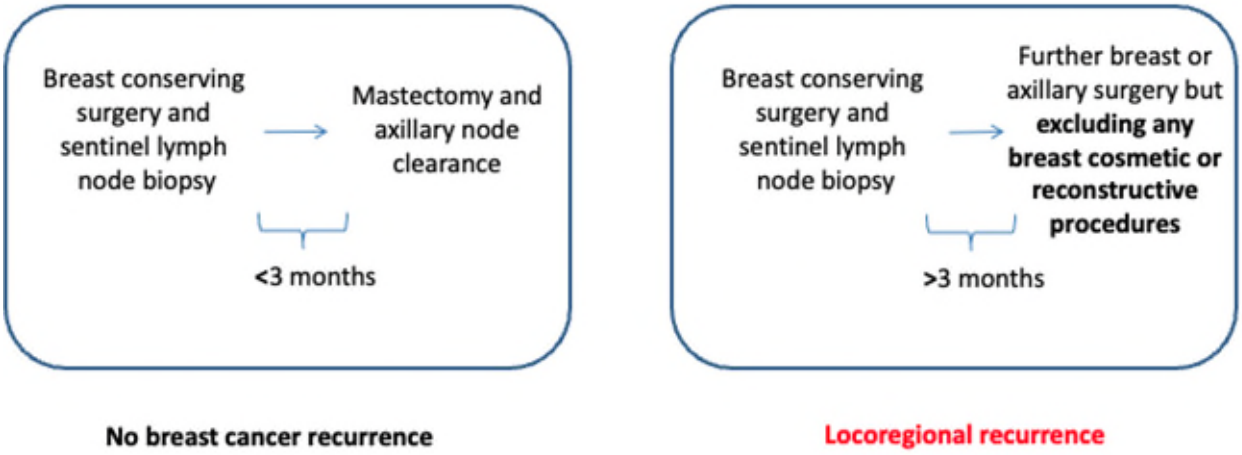



**Figure S1. (a) Example of initial coding rule used to help differentiate breast cancer recurrence from standard clinical care pathway based on the time period between certain procedures. (b) Example of refinement of initial coding rule following findings from the training exercise using 150 women from the AZURE trial.**

**Text S1: Summary of classifications used to derive outcomes for algorithm based on routinely collected data.**

The following text describes, for each of the outcomes recorded in the WMCIU database (listed in Table S1), the items in the routinely collected data (RCD) that were taken to indicate that the outcome had occurred. It necessarily refers to other coding schemes (OPCS4, ICD-10, ICD-9, SNOMED, NICIP). The relevant codes from these schemes are listed in Tables S2a-S2g & S3 and references to the manuals for the coding schemes are listed at the end of Table S2g. Additional abbreviations used in the text below are: COSD, Cancer Outcomes and Services Dataset; CWT, Cancer Waiting Times; HES, Hospital Episode Statistics; NMSC, Non-melanoma skin cancer; NEC, not elsewhere classified; RTDS, Radiotherapy Dataset; SACT, Systemic Anti-Cancer Therapy; DID, Diagnostic Imaging Dataset

## C01 – Death from breast cancer

Breast cancer (ICD-10 code: C50, ICD-9 code: 174) entered in any of the following death certification cause of death fields: 1a, 1b, 1c or 'underlying'. Breast cancer (ICD-10 code: C50, ICD-9 code: 174), 'Breast unspecified' or 'malignant neoplasm' that only appears in cause of death field 2 is not included.

This code is further subdivided based on whether there is evidence that the patient underwent breast surgery (into codes ***C01a – Death from breast cancer, having had breast surgery***; and ***C01b – Death from breast cancer but has never had breast surgery***). For this subdivision, breast surgery is determined if the patient has code '01' (first definitive treatment for a new primary cancer) in the cancer treatment event type variable in COSD/CWT or any of the OPCS4 codes in Supplementary Table S2a from HES.

## C03 – Distant metastases

Distant metastases classifications are subdivided into 4 categories:

**C03a(i): Distant metastases of liver/lung/bone/brain after 3 months**

Sites of secondary cancer defined as

| Cancer site | ICD-10 codes |
|---|---|
| Liver | C78.7 |
| Lung | C78.0, C78.1, C78.2 |
| Bone | C79.5 |
| Brain | C79.3, C79.4 |

Indicated by one or more of the following occurring at least 3 months after date of original cancer diagnosis in these 4 anatomical sites:

- COSD: Type of recurrence indicates metastatic disease ('05')

- CWT: if there is any information regarding metastases site or the cancer treatment event type is one of the following:

'05' Treatment for a distant recurrence of cancer (metastatic disease)

'07' First treatment for metastatic disease following an unknown primary

'08' Second or subsequent treatment for metastatic disease following an unknown primary

- HES: All women regarded as stage IV from the HES diagnosis codes (ICD-10 codes C77-C79) using criteria listed in Supplementary Table S3.

**C03a(ii): Distant metastases in other locations after 3 months**

There is a registration of a new secondary malignancy in an anatomical site not covered by C03a that occurs at least 93 days after the date of the original diagnosis.

**C03a(iii): Palliative care after 3 months**

Rationale: Palliative care is only given to cancer patients with distant metastases, so anyone receiving it after 3 months from diagnosis can be classified as C3a (i.e. confirmed distant metastasis).

Palliative care indicated if any of the following event codes are recorded for the cancer treatment modality (CWT/COSD):

'07' – specialist palliative care (CWT),

'09' – non-specialist palliative care (CWT).

**C03b: Distant metastases of liver/lung/bone/brain (unconfirmed) after 3 months**

Women who do not have any other invasive cancer recorded, excluding NMSC, (ICD-10 codes: C00-C97, including C50, but excluding C44; ICD-9 codes: 140-209, including 174, but excluding 173) but have one or more of the OPCS4 codes listed in Supplementary Table S2b, recorded in COSD/HES after 12 months of diagnosis, irrespective of the laterality of the procedure. However, with the following exceptions:

| **Exception** | **Rationale** |
|---|---|
| If OPCS4 codes ‘L912’ (Insertion of central venous catheter NEC) or ‘L913’ (Attention to central venous catheter NEC) occur within 400 days (approximately 13 months) of June 2005 | These codes are likely to be generated by Trastuzumab treatment, which was introduced around June 2005 and is administered every 3 weeks with a standard treatment duration of 12 months. |
| If OPCS4 code W085 (Partial excision of bone NEC) is combined with HES diagnosis code M751 (Rotator cuff syndrome) or M77 (Other enthesopathies) | Likely to be a routine removal of bone as part of orthopaedic surgery for musculoskeletal conditions and not a distant recurrence |

Women in C03b may either have (1) one or more of the cancers in C08a that was not registered, (2) an occult breast cancer recurrence or (3) no second cancer. The

classification algorithm will be re-run on these women after excluding the 'first event' to see which category they subsequently fall into.

## C07 – Cancer in the contralateral breast or the contralateral lymph nodes

This is also referred to as the woman having had bilateral breast cancer. Indicated by one or more of the following:

- COSD: Another, later breast tumour with different laterality

- HES: OPCS4 code for sentinel lymph node biopsy (see exception below), sampling or axillary dissection (see Supplementary Table S2a) **AND** the laterality relating to the event is not the same as recorded for the tumour.

- HES/COSD: OPCS4 code for breast conserving surgery or mastectomy (see Supplementary Table S2a) **AND** the laterality relating to the event is not the same as recorded for the tumour.

However, with the following exception:

| **Exception** | **Rationale** |
|---|---|
| An excision or biopsy of axillary lymph node (i.e. HES OPCS4 code 'T873') is not considered to indicate a contralateral breast cancer. | A biopsy without any further surgery/treatment is likely to be benign. |
| If a code for bilateral procedure (i.e. HES OPCS4 code 'Z941') is present and accompanied by any of the breast reconstruction OPCS4 codes listed in Supplementary Table S2c, then this is not counted as a contralateral breast cancer. | Breast reconstruction should not indicate a recurrence. |
| If the term 'prophylactic' surgery (i.e. ICD-10 codes listed in Supplementary Table S2d) from the HES data is present and in the absence of a new diagnosis of invasive breast cancer, then this will not be considered a contralateral breast recurrence. | Risk-reducing surgery (e.g. for genetic predisposition) with a cancer diagnosis, follow-up appointments relating to reconstructive or cosmetic procedures and wound-care related follow-up should not indicate a recurrence. |

## C04 – Recurrence of cancer in regional lymph nodes

Classifications for recurrences in the regional lymph nodes are subdivided into 2 categories, based on whether laterality is recorded:

### C04a: Recurrence of cancer in the ipsilateral regional lymph nodes

Indicated by one or more of the following occurring at least 6 months after date of original cancer diagnosis:

- HES/COSD: OPCS4 code indicating surgery for nodes and metastases: i.e. OPCS4 codes for sentinel lymph node biopsy, sampling or axillary dissection

(see Supplementary Table S2a) **AND** the laterality relating to the event is the same as recorded for the tumour

- COSD/CWT: Treatment event type '04': Treatment for a regional recurrence of cancer

**C04b: Recurrence of cancer in the regional lymph nodes with no laterality recorded (assumed to be ipsilateral)**

Indicated by one or more of the events listed in category '**C04a**', occurring at least 6 months after date of original cancer diagnosis, but with no laterality recorded in any routinely collected dataset. In this setting it is assumed that the recurrence of cancer is in the ipsilateral regional lymph nodes, in the absence of evidence to the contrary.

However, with the following exception:

| **Exception** | **Rationale** |
|---|---|
| If there is a reconstructive surgery code (and not oncological surgery) on the same date, even if accompanied by mastectomy codes 'B274', 'B278' or 'B275'. The OPCS4 codes used to define reconstructive surgery are listed in Supplementary Table S2c. | In this situation the mention of nodal involvement was likely attributable to the incident surgery/encounter (and the diagnosis has been duplicated in subsequent encounters) rather than a formal new diagnosis |

## C05 – Recurrence of cancer in the ipsilateral breast

Indicated by one or more of the following occurring at least 3 months after date of original cancer diagnosis:

- COSD: Another, later breast tumour with same laterality

- COSD/CWT: event type of '03', i.e. Treatment for a local recurrence of a primary cancer.

- HES/COSD: OPCS4 code for breast conserving surgery or mastectomy (see Supplementary Table S2a) **AND** the laterality relating to the event is the same as recorded for the original tumour, **AND** surgery is not within 6 months of the last date of neo-adjuvant chemotherapy.

However, with the following exception:

| **Exception** | **Rationale** |
|---|---|
| If there is a reconstructive surgery code (and not oncological surgery) on the ipsilateral side of previous breast surgery, even if accompanied by mastectomy codes 'B274', 'B278' or 'B275'. The OPCS4 codes used to define reconstructive surgery are listed in Supplementary Table S2c. | In this situation the mention of nodal involvement was likely attributable to the incident surgery/encounter (and the diagnosis has been duplicated in subsequent encounters) rather than a formal new diagnosis |

**C06 – Breast cancer recurrence of unknown location**

Indicated by one or more of the following:

- CWT: Variable for cancer or symptomatic breast referral patient status indicates that recurrent cancer is suspected or confirmed, i.e. one of the following is present:

  ‘15’ Suspected recurrent cancer

  ‘16’ Diagnosis of recurrent cancer confirmed - first NHS funded treatment not yet planned

  ‘17’ Diagnosis of recurrent cancer confirmed - NHS funded first treatment planned

  ‘18’ Diagnosis of recurrent cancer confirmed - no NHS funded treatment planned

  ‘19’ Diagnosis of recurrent cancer confirmed – subsequent NHS funded treatment not yet planned

  ‘20’ Diagnosis of recurrent cancer confirmed - subsequent NHS funded treatment planned

- COSD/CWT: Variable for cancer treatment event type has one of the following values:

  '06' Treatment for multiple recurrence of cancer (local/regional/distant)

  '09' 2nd or subsequent treatment for relapse of primary cancer

  '10' 2nd or subsequent treatment for progression of primary cancer

  '99'/'U' Unknown recurrence treatment

- COSD: recurrence flag = 'Y'

- COSD/CWT/RTDS: Initiation of radiotherapy ≥1 year after diagnosis (see Supplementary Table S2e for codes used to identify radiotherapy)

- COSD/HES/CWT/SACT: Initiation of chemotherapy ≥ 1 year after diagnosis (see Supplementary Table S2e for codes used to identify chemotherapy)

- COSD/CWT/SACT: Initiation of hormone therapy at any time after diagnosis following an absence of hormone therapy of ≥ 1 year (see Supplementary Table S2e for codes used to identify hormone therapy)

- COSD: Two or more of the following types of scan, within a 1 year time period, at least one year following diagnosis of breast cancer: ‘CT scan with contrast’, ‘CT scan with unspecified contrast’, ‘MRI scan with contrast’, ‘MRI scan with unspecified contrast’, ‘PET scan’, ‘Radio-isotope bone scan’.

- DID: Two or more of the types of scan listed in Supplementary Table S2f, within a 1 year time period, at least one year following diagnosis of breast cancer, OR one or more of the codes listed in Supplementary Table S2g after 1 year of diagnosis.

However, with the following exceptions:

| Exception | Rationale |
|---|---|
| If there is a 21 day repeating cycle of treatment **AND** the first '21 day event' starts within 400 days (approx. 13m) of first surgery/diagnosis or June 2005,<br>**AND** the total of '21 day events' ≥ 13<br>**AND** is within a 450 day period from first '21 day event'. | This treatment regimen is likely to be Trastuzumab. It was only until after June, 2005, Trastuzumab for HER2+ disease, was given in accordance with standard protocols. |
| The first SACT event is within 183 days (6m) of first surgery/diagnosis<br>**AND** there are ≥ 5 SACT events separated by <31 days in the first year since the first SACT event<br>**AND** ≥ 3 SACT events separated by 2-4 months in the second year since first SACT event. | This treatment pattern indicates possible zoledronic acid treatment but was stopped early. |
| One or two SACT or HES chemotherapy events occurring in the same week without another chemotherapy event in the preceding 5 months or subsequent 5 months | Likely artefactual |
| If a **C06** code is indicated along with the occurrence of any other invasive cancer (ICD-10 codes: C00-C97, including C50, but excluding C44; ICD-9 codes: 140-209, including 174, but excluding 173), then the **C08** code should take precedent. | |

## C08 – New primary cancer after 3 months

A new primary cancer is defined as the occurrence of any other invasive cancer (ICD-10 codes: C00-C97, including C50, but excluding C44; ICD-9 codes: 140-209, including 174, but excluding 173) as recorded in COSD.

New primary cancers are subdivided into three groups:

### C08a: New microscopically confirmed primary cancer of liver/lung/bone/brain after 3 months

Site of new cancer defined as

| Cancer site | ICD-9 code | ICD-10 code |
|---|---|---|
| Liver | 155 | C22 |
| Lung | 162 | C33-34 |
| Bone | 170 | C40-41 |
| Brain | 191-192 | C70-72 |

**AND** the cancer is considered microscopically confirmed if one or more of the following codes are recorded within 'basis of diagnosis':

- specific tumour markers
- cytology
- histology of metastasis
- histology of primary

**C08b: New microscopically unconfirmed primary cancer of liver/lung/bone/brain after 3 months**

Site of new cancer is defined as in **C08a**.

**AND** the cancer is considered microscopically unconfirmed if one or more of the following codes are recorded within 'basis of diagnosis':

- death certificate
- clinical
- clinical investigation
- x not known

**C08c: New primary cancer in other locations after 3 months**

Women falling into category **C08** who have invasive cancers other than those listed in **C08a** irrespective of the 'basis of diagnosis'.

## C09 – Death from cancer other than breast cancer

Any malignant cancer code (ICD-10 codes: C00-C97, ICD-9 codes: 140-209) excluding breast cancer (ICD-10 code: C50, ICD-9 code: 174) entered in any cause of death field 1a, 1b, 1c or 'underlying'. Codes in cause of death field 2 are not taken into account.

## C10 – Death where no cause has been attributed

When there is no information entered in any cause of death field 1a, 1b, 1c, 2 or 'underlying'.

## C11 – Death from cause other than cancer

No mention of cancer (ICD-10 codes: C00-C97, ICD-9 codes: 140-209) entered in any cause of death field 1a, 1b, 1c or 'underlying'. Codes in cause of death field 2 are not taken into account.

**Tables S2a-g: Summaries of code groupings used to derive outcomes for algorithm based on routinely collected data.**

**Table S2a: OPSC4[1] codes used to identify types of breast cancer surgery**

| Type of breast surgery | OPCS4 code | OPCS4 code description |
|---|---|---|
| Breast conserving surgery | B281 | Quadrantectomy of breast |
| | B282 | Partial excision of breast NEC |
| | B283 | Excision of lesion of breast NEC |
| | B285 | Wire guided partial excision of breast |
| | B286 | Excision of accessory breast tissue |
| | B287 | Wire guided excision of lesion of breast |
| | B288 | Other specified other excision of breast |
| | B289 | Unspecified other excision of breast |
| | B34 | Operations on duct of breast |
| | B341 | Subareolar excision of mammary duct |
| | B342 | Excision of mammary duct NEC |
| | B343 | Excision of lesion of mammary duct |
| | B344 | Microdochotomy |
| | B345 | Exploration of mammary duct NEC |
| | B348 | Other specified operations on duct of breast |
| | B349 | Unspecified operations on duct of breast |
| | B35 | Operations on nipple |
| | B351 | Transposition of nipple |
| | B352 | Excision of nipple |
| | B353 | Extirpation of lesion of nipple |
| | B354 | Plastic operations on nipple |
| | B355 | Biopsy of lesion of nipple |
| | B356 | Eversion of nipple |
| | B358 | Other specified operations on nipple |
| | B359 | Unspecified operations on nipple |
| | | |
| Mastectomy | B27 | Total excision of breast |
| | B271 | Total mastectomy and excision of both pectoral muscles and part of chest wall |
| | B272 | Total mastectomy and excision of both pectoral muscles NEC |
| | B273 | Total mastectomy and excision of pectoralis minor muscle |
| | B274 | Total mastectomy NEC |
| | B275 | Subcutaneous mastectomy |
| | B276 | Skin sparing mastectomy |
| | B278 | Other specified total excision of breast |
| | B279 | Unspecified total excision of breast |

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(Table S2a cont.)

| | | |
|---|---|---|
| SLNB | O142 | Sentinel lymph node |
| | T87 | Excision or biopsy of lymph node |
| | T873 | Excision or biopsy of axillary lymph node |
| | T878 | Other specified excision or biopsy of lymph node |
| | T879 | Unspecified excision or biopsy of lymph node |
| | T91 | Operations on sentinel lymph node |
| | T911 | Biopsy of sentinel lymph node NEC |
| | T918 | Other specified operations on sentinel lymph node |
| | T919 | Unspecified operations on sentinel lymph node |
| | T928 | Other specified other operations on lymphatic tissue |
| | Z613 | Axillary lymph node |
| | | |
| Sampling | T86 | Sampling of lymph nodes |
| | T862 | Sampling of axillary lymph nodes |
| | T869 | Unspecified sampling of lymph nodes |
| | | |
| Axillary Dissection | Z613 | Axillary lymph node |
| | T852 | Block dissection of axillary lymph nodes |
| | T859 | Unspecified block dissection of lymph nodes |

**Table S2b: OPSC4[1] codes for procedures that are likely a result of distant metastases of liver/lung/bone/brain**

| Operation site or type | OPCS4 code | OPCS4 code description |
|---|---|---|
| Liver | J023 | Resection of segment of liver |
| | J024 | Wedge excision of liver |
| | J027 | Extended left hemihepatectomy |
| | J029 | Unspecified partial excision of liver |
| | J031 | Excision of lesion of liver NEC |
| | J032 | Destruction of lesion of liver NEC |
| | J124 | Percutaneous radiofrequency ablation of lesion of liver |
| | | |
| Lung | T013 | Excision of lesion of chest wall |
| | T018 | Other specified partial excision of chest wall |
| | T019 | Unspecified partial excision of chest wall |
| | T078 | Other specified open excision of pleura |
| | T079 | Unspecified open excision of pleura |
| | T094 | Chemical open pleurodesis |
| | T095 | Open pleurodesis NEC |
| | T101 | Endoscopic extirpation of lesion of pleura |
| | T102 | Endoscopic pleurodesis using talc |
| | T103 | Endoscopic pleurodesis NEC |
| | T121 | Drainage of lesion of pleura NEC |
| | T122 | Drainage of pleural cavity NEC |
| | T124 | Insertion of tube drain into pleural cavity |
| | T131 | Insufflation of talc into pleural cavity NEC |
| | E541 | Total pneumonectomy |
| | E542 | Bilobectomy of lung |
| | E543 | Lobectomy of lung |
| | E544 | Excision of segment of lung |
| | E545 | Partial lobectomy of lung NEC |
| | E548 | Other specified excision of lung |
| | E552 | Open excision of lesion of lung |
| | E558 | Other specified open extirpation of lesion of lung |
| | | |
| Bone | W085 | Partial excision of bone NEC |
| | W088 | Other specified other excision of bone |
| | W089 | Unspecified other excision of bone |
| | W091 | Excision of lesion of bone NEC |
| | W093 | Curettage of lesion of bone NEC |
| | W096 | Curettage of tumour of bone NEC |
| | W097 | Excision of tumour of bone |
| | W098 | Other specified extirpation of lesion of bone |
| | W099 | Unspecified extirpation of lesion of bone |
| | V257 | Primary anterior corpectomy of lumbar spine and reconstruction HFQ |
| | V431 | Excision of lesion of cervical vertebra |
| | V432 | Excision of lesion of thoracic vertebra |

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(Table S2b cont.)

| | | |
|---|---|---|
| Brain | A021 | Excision of lesion of tissue of frontal lobe of brain |
| | A022 | Excision of lesion of tissue of temporal lobe of brain |
| | A023 | Excision of lesion of tissue of parietal lobe of brain |
| | A024 | Excision of lesion of tissue of occipital lobe of brain |
| | A025 | Excision of lesion of tissue of cerebellum |
| | A026 | Excision of lesion of tissue of brain stem |
| | A028 | Other specified excision of lesion of tissue of brain |
| | A029 | Unspecified excision of lesion of tissue of brain |
| | A178 | Other specified therapeutic endoscopic operations on ventricle of brain |
| | V051 | Extirpation of lesion of cranium |
| | | |
| Other | B343 | Excision of lesion of mammary duct |
| | B401 | Interstitial laser destruction of lesion of breast |
| | Q241 | Salpingo ophorectomy NEC |
| | S049 | Unspecified other excision of skin |
| | T882 | Drainage of lesion of axillary lymph node |
| | L912 | Insertion of central venous catheter NEC |
| | L913 | Attention to central venous catheter NEC |
| | L915 | Insertion of tunnelled venous catheter |
| | L943 | Percutaneous transluminal insertion of subcutaneous port |

**Table S2c: OPSC4[1] codes used to identify types of breast reconstructive surgery**

| OPCS4 code | OPCS4 code description |
|---|---|
| B291 | Reconstruction of breast using myocutaneous flap of latissimus dorsi muscle |
| B293 | Reconstruction of breast using flap of skin of abdomen NEC |
| B295 | Revision of reconstruction of breast |
| B298 | Other specified reconstruction of breast |
| B299 | Unspecified reconstruction of breast |
| B301 | Insertion of prosthesis for breast |
| B302 | Revision of prosthesis for breast |
| B303 | Removal of prosthesis for breast |
| B304 | Renewal of prosthesis for breast |
| B308 | Other specified prosthesis for breast |
| B309 | Unspecified prosthesis for breast |
| B311 | Reduction mammoplasty |
| B312 | Augmentation mammoplasty |
| B313 | Mastopexy |
| B314 | Revision of mammoplasty |
| B318 | Other specified other plastic operations on breast |
| B319 | Unspecified other plastic operations on breast |
| B354 | Plastic operations on nipple |
| B358 | Other specified operations on nipple |
| B374 | Capsulectomy of breast |
| B375 | Lipofilling of breast |
| B378 | Other specified other operations on breast |
| B379 | Unspecified other operations on breast |
| B381 | Reconstruction of breast using free superior gluteal artery perforator flap |
| B382 | Reconstruction of breast using free inferior gluteal artery perforator flap |
| B388 | Other specified reconstruction of breast using flap of skin of buttock |
| B389 | Unspecified reconstruction of breast using flap of skin of buttock |
| B391 | Reconstruction of breast using free transverse rectus abdominis myocutaneous flap |
| B392 | Reconstruction of breast using pedicled transverse rectus abdominis myocutaneous flap |
| B393 | Reconstruction of breast using free deep inferior epigastric perforator flap |
| B394 | Reconstruction of breast using pedicled omental flap |
| B395 | Reconstruction of breast using free omental flap |
| B398 | Other specified reconstruction of breast using abdominal flap |
| B399 | Unspecified reconstruction of breast using abdominal flap |

**Table S2d: ICD-10 codes[2] used to identify types of prophylactic surgery**

| ICD-10 code | ICD-10 code description |
|---|---|
| Z400 | Prophylactic surgery for risk-factors related to malignant neoplasms |
| Z421 | Follow-up care involving plastic surgery of breast |
| Z422 | Follow-up care involving plastic surgery of other parts of trunk |
| Z429 | Follow-up care involving plastic surgery, unspecified |
| Z443 | Fitting and adjustment of external breast prosthesis |
| Z418 | Other procedures for purposes other than remedying health state |
| Z419 | Procedure for purposes other than remedying health state, unspecified |
| Z480 | Attention to surgical dressings and sutures |
| Z488 | Other specified surgical follow-up care |
| Z489 | Surgical follow-up care, unspecified |

**Table S2e: Codes used to identify types of breast cancer treatment.**

| Treatment type | Dataset and code type | Code | Code description |
|---|---|---|---|
| Chemo-therapy | COSD/HES - OPCS4 codes | X70 | Procurement of drugs for chemotherapy for neoplasm in Bands 1-5 |
| | | X71 | Procurement of drugs for chemotherapy for neoplasm in Bands 6-10 |
| | | X72 | Delivery of chemotherapy for neoplasm |
| | | X73 | Delivery of oral chemotherapy for neoplasm |
| | | X74 | Other chemotherapy drugs |
| | | X28 | Intermittent infusion of therapeutic substance |
| | | X29 | Continuous Infusion of therapeutic substance |
| | | X35 | Other intravenous injection |
| | | X37 | Intramuscular injection |
| | | X38 | Subcutaneous injection |
| | | X89 | High cost immunosuppressant drugs |
| | | | |
| | HES - ICD-10 diagnosis code | Z511 | Chemotherapy session for neoplasm |
| | | | |
| | CWT/COSD-Cancer treatment modality variable | 02 | Anti-cancer drug regimen (Cytotoxic Chemotherapy) |
| | | 14 | Anti-cancer drug regimen (other) |
| | | | |
| Radio-therapy | COSD/HES - OPCS4 codes | X65 | Radiotherapy delivery |
| | | | |
| | CWT/COSD-Cancer treatment modality variable | 05 | Teletherapy (Beam Radiation excluding Proton Therapy) |
| | | 06 | Brachytherapy |
| | | 22 | Radiosurgery |
| | | | |
| Hormone therapy | CWT/COSD-Cancer treatment modality variable | 03 | Anti-cancer drug regimen (Hormone Therapy) |
| | | | |
| Immuno-therapy | CWT/COSD-Cancer treatment modality variable | 15 | Anti-cancer drug regimen (Immunotherapy) |

**Table S2f: DID procedure codes (SNOMED[3] and NICIP[4]) within the first year after diagnosis.**

| Procedure (SNOMED description) | SNOMED code (SCT-ID) | NICIP code |
|---|---|---|
| Computed tomography of abdomen | 169070004 | CABDO |
| Computed tomography and biopsy of abdomen | 419940006 | CABDOB |
| Computed tomography of abdomen and pelvis | 419394006 | CABPE |
| Computed tomography of chest and abdomen | 418891003 | CCABD |
| Computed tomography of chest, abdomen and pelvis | 418023006 | CCHAP |
| Computed tomography of chest | 169069000 | CCHES |
| Computed tomography of cervical spine | 241578008 | CCSPN |
| Computed tomography of liver | 241549007 | CLIVE |
| Computed tomography and biopsy of liver | 418749009 | CLIVEB |
| Computed tomography of lumbar spine | 241580002 | CLSPN |
| Computed tomography of mediastinum | 241543008 | CMEDM |
| Computed tomography of pituitary fossa | 241519005 | CPITF |
| Computed tomography of posterior fossa | 241518002 | CPOSF |
| Computed tomography of sacral spine | 241581003 | CSACM |
| Computed tomography of thoracic spine | 241579000 | CTSPN |
| Virtual computed tomography bronchoscopy | 418419008 | CVBRY |
| Magnetic resonance imaging of abdomen | 241621009 | MABDO |
| Ablation of lesion of liver using computed tomography guidance | 432226009 | CLMAAA |
| Radiofrequency ablation of lesion of liver using computed tomography guidance | 431475009 | CLMAFA |
| Laser ablation of lesion of liver using computed tomography guidance | 433866007 | CLMASA |
| Computed tomography of neck and thorax | 430448007 | CNECH |
| Computed tomography of neck and thorax with contrast | 429927002 | CNECHC |
| Computed tomography of neck with contrast | 431326009 | CNECKC |
| Computed tomography of sacral spine with contrast | 430452007 | CSACMC |
| Computed tomography of sternum | 429874005 | CSTRM |
| Magnetic resonance imaging of chest with contrast | 432815006 | MCHESC |
| Magnetic resonance imaging of liver with contrast | 431839003 | MLIVEC |

**Table S2g: DID procedure codes (SNOMED[3] and NICIP[4]) at least one year following diagnosis.**

| Procedure (SNOMED description) | SNOMED code (SCT-ID) | NICIP code |
|---|---|---|
| Computed tomography of breast for radiotherapy planning | 429866009 | CRTMAR |
| Computed tomography of head for radiotherapy planning | 429867000 | CRTSKR |
| Computed tomography of spine for radiotherapy planning | 430438005 | CRTSPR |
| Magnetic resonance imaging of chest for radiotherapy planning | 431766006 | MRTCHR |
| Magnetic resonance imaging of breast for radiotherapy planning | 430243000 | MRTMAR |
| Radiofrequency ablation using ultrasound guidance | 433058002 | URAFGA |
| Wire guided localisation of lesion using ultrasonography guidance | 915381000000106 | UWLLE |
| Wire guided localisation of breast lesion using magnetic resonance imaging guidance | 911831000000104 | MWLBL |
| Wire guided localisation of breast lesion using magnetic resonance imaging guidance | 911831000000104 | MWLBR |
| Wire guided localisation of breast lesion using magnetic resonance imaging guidance | 911831000000104 | MWLBB |
| Biopsy of femur using fluoroscopic guidance | 431455000 | FTHIBB |
| Biopsy of lung using computed tomography guidance | 429932001 | CLUNGB |
| Biopsy of brain using computed tomography guidance | 432666003 | CSKUHB |

**References**


1. **OPCS4:** NHS Digital, *National Clinical Coding Standards OPCS-4.* Accurate data for quality information, 2022. Version: [9.1].

2. **ICD:** World Health Organization. *International Statistical Classification of Diseases and Related Health Problems*
*10th Revision.* 2019 [cited 2024 23/07/2024]; Available from: https://icd.who.int/browse10/2019/en.
*9th Revision. 1975*. World Health Organisation: Geneva

3. **SNOMED:** International Health Terminology Standards Development Organisation. *SNOMED Clinical Terms.* 2007 [cited 2024 23/07/2024]; Available from: https://www.snomed.org/.

*4.* **NICIP:** *National Interim Clinical Imaging Procedure (NICIP) Code Set. NICIP code set* 2016 [cited 2024 23/07/2024]; Available from: https://digital.nhs.uk/services/terminology-and-classifications/national-interim-clinical-imaging-procedure-nicip-code-set.

**Table S3: For women registered as stage VI (unknown stage), ICD-10 codes C77-C79 from HES data (within 3 months of diagnosis of breast cancer) were used to determine cancer stage.**

| ICD-10 code | Sub-classification | Cancer stage to be allocated |
|---|---|---|
| C77 Secondary and unspecified malignant neoplasm of lymph nodes | C77.0 Lymph nodes of head, face and neck Supraclavicular lymph nodes | II |
| | C77.1 Intrathoracic lymph nodes | II |
| | C77.2 Intra-abdominal lymph nodes | VI (Not staged) |
| | C77.3 Axillary and upper limb lymph nodes Pectoral lymph nodes | II |
| | C77.4 Inguinal and lower limb lymph nodes | VI (Not staged) |
| | C77.5 Intrapelvic lymph nodes | VI (Not staged) |
| | C77.8 Lymph nodes of multiple regions | II |
| | C77.9 Lymph node, unspecified | II |
| C78 Secondary malignant neoplasm of respiratory and digestive organs | C78.0 Secondary malignant neoplasm of lung | IV |
| | C78.1 Secondary malignant neoplasm of mediastinum | IV |
| | C78.2 Secondary malignant neoplasm of pleura Malignant pleural effusion NOS | IV |
| | C78.3 Secondary malignant neoplasm of other and unspecified respiratory organs | IV |
| | C78.4 Secondary malignant neoplasm of small intestine | VI (Not staged) |
| | C78.5 Secondary malignant neoplasm of large intestine and rectum | VI (Not staged) |
| | C78.6 Secondary malignant neoplasm of retroperitoneum and peritoneum, Malignant ascites NOS | IV |
| | C78.7 Secondary malignant neoplasm of liver and intrahepatic bile duct | IV |
| | C78.8 Secondary malignant neoplasm of other and unspecified digestive organs | IV |
| C79 Secondary malignant neoplasm of other and unspecified sites | C79.0 Secondary malignant neoplasm of kidney and renal pelvis | VI (Not staged) |
| | C79.1 Secondary malignant neoplasm of bladder and other and unspecified urinary organs | VI (Not staged) |
| | C79.2 Secondary malignant neoplasm of skin | IV |
| | C79.3 Secondary malignant neoplasm of brain and cerebral meninges | IV |
| | C79.4 Secondary malignant neoplasm of other and unspecified parts of nervous system | IV |
| | C79.5 Secondary malignant neoplasm of bone and bone marrow | IV |
| | C79.6 Secondary malignant neoplasm of ovary | VI (Not staged) |
| | C79.7 Secondary malignant neoplasm of adrenal gland | VI (Not staged) |
| | C79.8 Secondary malignant neoplasm of other specified sites | IV |
| | C79.9 Secondary malignant neoplasm, unspecified site, Carcinomatosis (secondary), Disseminated (secondary): cancer NOS, malignancy NOS, Generalized (secondary): cancer NOS, Malignancy NOS, Multiple secondary cancer NOS, Sarcomatosis (secondary) NOS | IV |

**Table S4: Summary of the clinical events used for each of the different analysis outcomes considered.** Clinical events grouped according to Table S1.

| Analysis outcome | Events considered for analyses | | |
|---|---|---|---|
| | **Outcome events** | **Censored events**[a] | **Ignored events** |
| **Distant recurrence** | Distant metastases<br>Death from breast cancer | Non-breast-cancer malignancy<br>Non-breast-cancer death | Locoregional recurrence<br>Recurrence, type unknown[b]<br>Contralateral breast cancer |
| **Locoregional recurrence** | Locoregional recurrence | Distant metastases<br>Contralateral breast cancer<br>Non-breast-cancer malignancy<br>Any death | Recurrence, type unknown[b] |
| **Contralateral breast cancer** | Contralateral breast cancer | Distant metastases<br>Locoregional recurrence<br>Non-breast-cancer malignancy<br>Any death | Recurrence, type unknown[b] |
| **Any recurrence** | Locoregional recurrence<br>Distant metastases<br>Recurrence, type unknown[b]<br>Contralateral breast cancer<br>Death from breast cancer | Non-breast-cancer malignancy<br>Non-breast-cancer death | - |
| **Breast cancer mortality** | Death from breast cancer | Non-breast-cancer death | Locoregional recurrence<br>Recurrence, type unknown[b]<br>Contralateral breast cancer<br>Distant metastases<br>Non-breast-cancer malignancy |
| **All-cause mortality** | Death from breast cancer<br>Non-breast-cancer death | - | Locoregional recurrence<br>Recurrence, type unknown[b]<br>Contralateral breast cancer<br>Distant metastases<br>Non-breast-cancer malignancy |
| **Any recurrence: Post-validation adjustment** | ***All time periods:***<br>Distant metastases<br>Death from breast cancer<br>***After first year from diagnosis:***<br>Locoregional recurrence<br>Recurrence, type unknown[b]<br>Contralateral breast cancer | Non-breast-cancer malignancy<br>Non-breast-cancer death | ***Within first year after diagnosis:***<br>Locoregional recurrence<br>Recurrence, type unknown[b]<br>Contralateral breast cancer |

[a] Women were removed from the analysis when a censored event occurred
[b] Event code not present in AZURE trial data

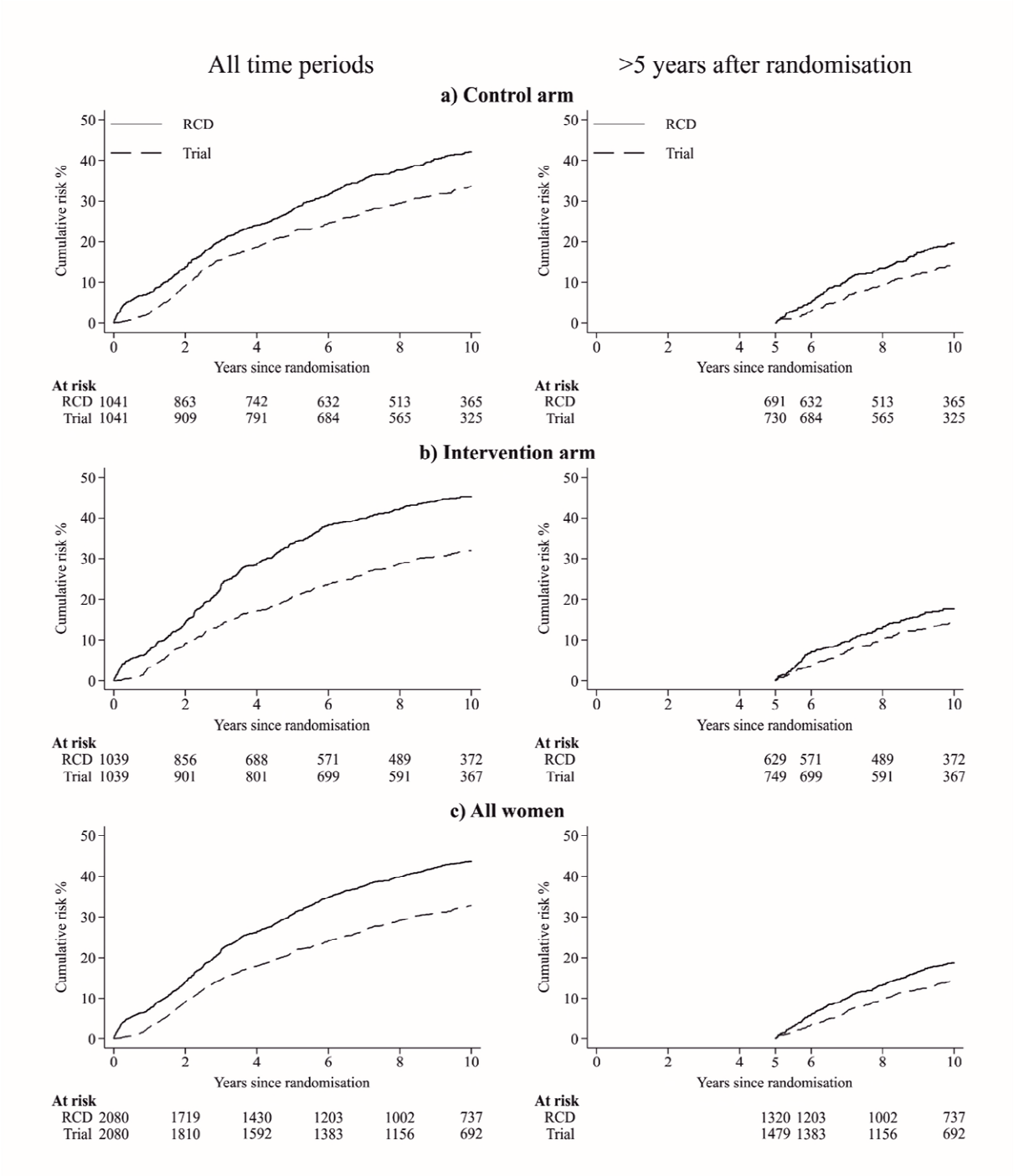


**Figure S2. External validation exercise: Cumulative risk of distant recurrence in AZURE trial (dashed lines) and in the routinely collected data (RCD) (solid lines). Analyses are by separate randomisation arm (a and b), and for all 2080 women included in the external validation group (c).** The outcome of distant recurrence is defined in Table S4. Plotted values at 1-, 3-, 5- and 10-years (and 95% confidence intervals) are in Table S5.

**Table S5. External validation exercise: Number of events and cumulative risks of distant recurrence by time since randomisation and AZURE trial arm, for routinely collected data (RCD) and AZURE trial data.** Calculated for all 2080 women in the external validation cohort.

| | | | All time periods | | | >5 years after randomisation | | |
|---|---|---|---|---|---|---|---|---|
| **Trial Arm** | **Dataset** | **Time since randomisation (years)** | **No. women at risk[a]** | **No. events[b]** | **Cumulative risk[c] % (95% CI)** | **No. women at risk[a]** | **No. events[b]** | **Cumulative risk[c] % (95% CI)** |
| **Control** | RCD | 0-1 | 1041 | 76 | 7.3 (5.9, 9.1) | - | - | - |
| | | 1-3 | 952 | 131 | 20.3 (18.0, 22.9) | - | - | - |
| | | 3-5 | 789 | 73 | 27.8 (25.1, 30.7) | - | - | - |
| | | 5-10 | 691 | 121 | 42.6 (39.5, 45.9) | 691 | 121 | 20.6 (17.5, 24.1) |
| | Trial | 0-1 | 1041 | 25 | 2.4 (1.6, 3.6) | - | - | - |
| | | 1-3 | 995 | 131 | 15.4 (13.3, 17.8) | - | - | - |
| | | 3-5 | 840 | 65 | 22.2 (19.7, 24.9) | - | - | - |
| | | 5-10 | 730 | 93 | 34.8 (31.7, 38.1) | 730 | 93 | 16.2 (13.4, 19.5) |
| **Intervention** | RCD | 0-1 | 1039 | 77 | 7.5 (6.0, 9.3) | - | - | - |
| | | 1-3 | 941 | 159 | 23.3 (20.8, 26.1) | - | - | - |
| | | 3-5 | 757 | 99 | 33.6 (30.7, 36.6) | - | - | - |
| | | 5-10 | 629 | 103 | 46.0 (42.8, 49.2) | 629 | 103 | 18.7 (15.7, 22.2) |
| | Trial | 0-1 | 1039 | 33 | 3.2 (2.3, 4.5) | - | - | - |
| | | 1-3 | 981 | 106 | 13.8 (11.8, 16.1) | - | - | - |
| | | 3-5 | 847 | 65 | 20.6 (18.2, 23.2) | - | - | - |
| | | 5-10 | 749 | 97 | 33.3 (30.2, 36.5) | 749 | 97 | 16.0 (13.3, 19.2) |
| **Total** | RCD | 0-1 | 2080 | 153 | 7.4 (6.4, 8.6) | - | - | - |
| | | 1-3 | 1893 | 290 | 21.8 (20.1, 23.7) | - | - | - |
| | | 3-5 | 1546 | 172 | 30.7 (28.7, 32.7) | - | - | - |
| | | 5-10 | 1320 | 224 | 44.3 (42.0, 46.6) | 1320 | 224 | 19.6 (17.5, 22.1) |
| | Trial | 0-1 | 2080 | 58 | 2.8 (2.2, 3.6) | - | - | - |
| | | 1-3 | 1976 | 237 | 14.6 (13.2, 16.2) | - | - | - |
| | | 3-5 | 1687 | 130 | 21.4 (19.6, 23.2) | - | - | - |
| | | 5-10 | 1479 | 190 | 34.0 (31.8, 36.3) | 1479 | 190 | 16.1 (14.1, 18.3) |

[a] Number of women at risk at start of time category
[b] Number of events during time category
[c] Cumulative risk at end of time category

**Table S6. External validation exercise: Agreement of routinely collected data (RCD) and AZURE trial data for distant recurrence.**
Calculations performed for all 2080 women in external validation cohort. The outcome of distant recurrence is defined in Table S4.

| Distant recurrence[a] | Analysis period and trial arm | | | | | |
|---|---|---|---|---|---|---|
| | All time periods | | | >5 years after randomisation[b] | | |
| | Control (N=1041) | Intervention (N=1039) | Total (N=2080) | Control (N=1041) | Intervention (N=1039) | Total (N=2080) |
| | | | No. | | | |
| Event in both datasets | 294 | 289 | 583 | 71 | 65 | 136 |
| Event only in trial data | 23 | 15 | 38 | 14 | 10 | 24 |
| Event only in RCD | 110 | 149 | 259 | 32 | 26 | 58 |
| No event in either dataset | 614 | 586 | 1200 | 537 | 509 | 1046 |
| **Censored before analysis period** | | | | | | |
| Only in trial data | 0 | 0 | 0 | 37 | 19 | 56 |
| Only in RCD | 0 | 0 | 0 | 76 | 139 | 215 |
| In both datasets | 0 | 0 | 0 | 274 | 271 | 545 |
| **Time difference when event present in both datasets** | | | **No. (%)** | | | |
| <6 months | 199 (67.7%) | 181 (62.6%) | 380 (65.2%) | 58 (81.7%) | 55 (84.6%) | 113 (83.1%) |
| 6-12 months | 37 (12.6%) | 39 (13.5%) | 76 (13.0%) | 9 (12.7%) | 5 (7.7%) | 14 (10.3%) |
| >1 year | 58 (19.7%) | 69 (23.9%) | 127 (21.8%) | 4 (5.6%) | 5 (7.7%) | 9 (6.6%) |
| **Performance measures[c]** | | | **% (95% CI)** | | | |
| *All time periods* | | | | | | |
| Sensitivity | 92.7 (89.9, 95.6) | 95.1 (92.6, 97.5) | 93.9 (92.0, 95.8) | 83.5 (75.6, 91.4) | 86.7 (79.0, 94.4) | 85.0 (79.5, 90.5) |
| Specificity | 84.8 (82.2, 87.4) | 79.7 (76.8, 82.6) | 82.2 (80.3, 84.2) | 94.4 (92.5, 96.3) | 95.1 (93.3, 97.0) | 94.7 (93.4, 96.1) |
| PPV | 72.8 (68.4, 77.1) | 66.0 (61.5, 70.4) | 69.2 (66.1, 72.4) | 68.9 (60.0, 77.9) | 71.4 (62.1, 80.7) | 70.1 (63.7, 76.5) |
| NPV | 96.4 (94.9, 97.8) | 97.5 (96.3, 98.8) | 96.9 (96.0, 97.9) | 97.5 (96.1, 98.8) | 98.1 (96.9, 99.3) | 97.8 (96.9, 98.6) |
| *Within 6 months of trial data* | | | | | | |
| Sensitivity | 62.8 (57.5, 68.1) | 59.5 (54.0, 65.1) | 61.2 (57.4, 65.0) | 68.2 (58.3, 78.1) | 73.3 (63.3, 83.3) | 70.6 (63.6, 77.7) |
| Specificity | 84.8 (82.2, 87.4) | 79.7 (76.8, 82.6) | 82.2 (80.3, 84.2) | 94.4 (92.5, 96.3) | 95.1 (93.3, 97.0) | 94.7 (93.4, 96.1) |
| PPV | 64.4 (59.1, 69.7) | 54.8 (49.5, 60.2) | 59.5 (55.7, 63.3) | 64.4 (54.6, 74.3) | 67.9 (57.7, 78.1) | 66.1 (59.0, 73.2) |
| NPV | 83.9 (81.2, 86.5) | 82.7 (79.9, 85.4) | 83.3 (81.3, 85.2) | 95.2 (93.5, 97.0) | 96.2 (94.6, 97.8) | 95.7 (94.5, 96.9) |

PPV, Positive predictive value; NPV, Negative predictive value

[a] Women are censored at non-breast cancer malignancies or non-breast-cancer deaths

[b] Analysis period starts at 5 years after randomisation

[c] Performance measures defined in footnote of Table 3

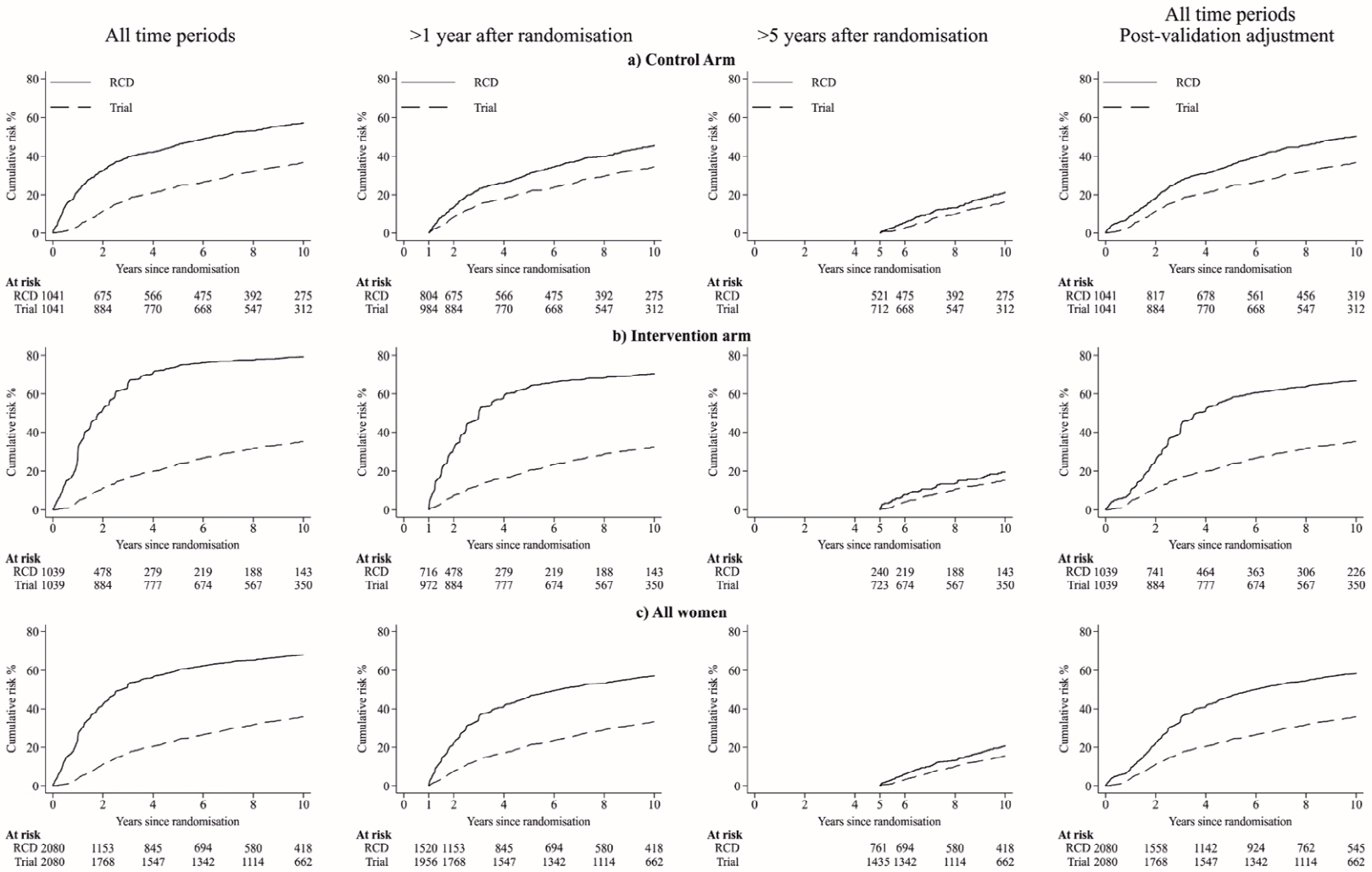


**Figure S3. External validation exercise: Cumulative risk of any recurrence in AZURE trial (dashed lines) and in routinely collected data (RCD) (solid lines). Analyses are by separate randomisation arm (a and b), and for all 2080 women included in external validation group (c).** The outcome of any recurrence is defined in Table S4. Plotted values at 1-, 3-, 5- and 10-years (and 95% confidence intervals) are in Table S7.

**Table S7. External validation exercise: Number of events and cumulative risks of any recurrence by time since randomisation and AZURE trial arm, for routinely collected data (RCD) and AZURE trial data.** Calculated for all 2080 women in the external validation cohort.

| Trial Arm and Dataset | Time since random-isation (years) | All time periods | | | >1 year after randomisation | | | >5 years after randomisation | | | All time periods with post-validation adjustment | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. women at risk[a] | No. events[b] | Cumulative risk[c] % (95% CI) | No. women at risk[a] | No. events[b] | Cumulative risk[c] % (95% CI) | No. women at risk[a] | No. events[b] | Cumulative risk[c] % (95% CI) | No. women at risk[a] | No. events[b] | Cumulative risk[c] % (95% CI) |
| **Control** | | | | | | | | | | | | | |
| RCD | 0-1 | 1041 | 225 | 21.7 (19.3, 24.4) | - | - | - | - | - | - | 1041 | 93 | 9.0 (7.4, 10.9) |
| | 1-3 | 804 | 180 | 39.5 (36.6, 42.6) | 804 | 180 | 22.8 (20.0, 25.8) | - | - | - | 935 | 184 | 27.2 (24.5, 30.0) |
| | 3-5 | 598 | 60 | 45.7 (42.7, 48.8) | 598 | 60 | 30.6 (27.5, 34.0) | - | - | - | 723 | 79 | 35.3 (32.4, 38.3) |
| | 5-10 | 521 | 98 | 57.6 (54.5, 60.8) | 521 | 98 | 45.8 (42.2, 49.6) | 521 | 98 | 21.9 (18.4, 26.1) | 621 | 128 | 50.8 (47.6, 54.1) |
| Trial | 0-1 | 1041 | 36 | 3.5 (2.5, 4.8) | - | - | - | - | - | - | 1041 | 36 | 3.5 (2.5, 4.8) |
| | 1-3 | 984 | 143 | 17.7 (15.5, 20.2) | 984 | 143 | 14.7 (12.6, 17.1) | - | - | - | 984 | 143 | 17.7 (15.5, 20.2) |
| | 3-5 | 817 | 64 | 24.3 (21.8, 27.1) | 817 | 64 | 21.6 (19.1, 24.3) | - | - | - | 817 | 64 | 24.3 (21.8, 27.1) |
| | 5-10 | 712 | 100 | 37.8 (34.6, 41.1) | 712 | 100 | 35.5 (32.4, 38.9) | 712 | 100 | 17.8 (14.9, 21.2) | 712 | 100 | 37.8 (34.6, 41.1) |
| **Intervention** | | | | | | | | | | | | | |
| RCD | 0-1 | 1039 | 308 | 29.9 (27.2, 32.8) | - | - | - | - | - | - | 1039 | 100 | 9.7 (8.1, 11.7) |
| | 1-3 | 716 | 353 | 64.9 (61.9, 67.8) | 716 | 353 | 49.9 (46.3, 53.7) | - | - | - | 918 | 329 | 42.5 (39.5, 45.6) |
| | 3-5 | 345 | 90 | 74.2 (71.5, 76.9) | 345 | 90 | 63.3 (59.7, 66.9) | - | - | - | 564 | 144 | 57.5 (54.4, 60.6) |
| | 5-10 | 240 | 44 | 79.6 (76.9, 82.1) | 240 | 44 | 70.8 (67.3, 74.3) | 240 | 44 | 20.6 (15.8, 26.7) | 399 | 80 | 67.1 (64.1, 70.1) |
| Trial | 0-1 | 1039 | 43 | 4.2 (3.1, 5.6) | - | - | - | - | - | - | 1039 | 43 | 4.2 (3.1, 5.6) |
| | 1-3 | 972 | 122 | 16.4 (14.2, 18.8) | 972 | 122 | 12.7 (10.8, 15.0) | - | - | - | 972 | 122 | 16.4 (14.2, 18.8) |
| | 3-5 | 825 | 70 | 23.6 (21.1, 26.4) | 825 | 70 | 20.3 (17.8, 23.0) | - | - | - | 825 | 70 | 23.6 (21.1, 26.4) |
| | 5-10 | 723 | 98 | 36.4 (33.3, 39.7) | 723 | 98 | 33.6 (30.5, 36.9) | 723 | 98 | 16.7 (13.9, 20.0) | 723 | 98 | 36.4 (33.3, 39.7) |
| **Total** | | | | | | | | | | | | | |
| RCD | 0-1 | 2080 | 533 | 25.8 (24.0, 27.7) | - | - | - | - | - | - | 2080 | 193 | 9.4 (8.2, 10.7) |
| | 1-3 | 1520 | 533 | 52.2 (50.0, 54.4) | 1520 | 533 | 35.6 (33.2, 38.1) | - | - | - | 1853 | 513 | 34.8 (32.8, 36.9) |
| | 3-5 | 943 | 150 | 59.9 (57.8, 62.1) | 943 | 150 | 46.0 (43.5, 48.6) | - | - | - | 1287 | 223 | 46.3 (44.1, 48.5) |
| | 5-10 | 761 | 142 | 68.5 (66.4, 70.6) | 761 | 142 | 57.6 (55.0, 60.2) | 761 | 142 | 21.5 (18.6, 24.8) | 1020 | 208 | 58.9 (56.7, 61.2) |
| Trial | 0-1 | 2080 | 79 | 3.8 (3.1, 4.8) | - | - | - | - | - | - | 2080 | 79 | 3.8 (3.1, 4.8) |
| | 1-3 | 1956 | 265 | 17.0 (15.5, 18.7) | 1956 | 265 | 13.7 (12.3, 15.3) | - | - | - | 1956 | 265 | 17.0 (15.5, 18.7) |
| | 3-5 | 1642 | 134 | 24.0 (22.1, 25.9) | 1642 | 134 | 20.9 (19.2, 22.8) | - | - | - | 1642 | 134 | 24.0 (22.1, 25.9) |
| | 5-10 | 1435 | 198 | 37.1 (34.9, 39.4) | 1435 | 198 | 34.6 (32.3, 36.9) | 1435 | 198 | 17.3 (15.2, 19.6) | 1435 | 198 | 37.1 (34.9, 39.4) |

[a] Number of women at risk at start of time category [b] Number of events during time category [c] Cumulative risk at end of time category

**Table S8. External validation exercise: Agreement of routinely collected data (RCD) and AZURE trial data for any recurrence.** Calculations performed for all 2080 women in external validation cohort. The outcome of any recurrence is defined in Table S4.

| Any recurrence | Analysis period and trial arm | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All time periods | | | >1 year after randomisation[a] | | | >5 years after randomisation[a] | | | All time periods with post-validation adjustment[b] | | |
| | Control (N=1041) | Intervention (N=1039) | Total (N=2080) | Control (N=1041) | Intervention (N=1039) | Total (N=2080) | Control (N=1041) | Intervention (N=1039) | Total (N=2080) | Control (N=1041) | Intervention (N=1039) | Total (N=2080) |
| | | | | | | No. | | | | | | |
| Event in both datasets | 340 | 328 | 668 | 227 | 185 | 412 | 65 | 27 | 92 | 338 | 327 | 665 |
| Event only in trial data | 6 | 8 | 14 | 6 | 7 | 13 | 4 | 4 | 8 | 8 | 9 | 17 |
| Event only in RCD | 226 | 469 | 695 | 103 | 286 | 389 | 28 | 14 | 42 | 190 | 451 | 641 |
| No event in either dataset | 469 | 234 | 703 | 454 | 219 | 673 | 407 | 187 | 594 | 505 | 252 | 757 |
| **Censored before analysis period** | | | | | | | | | | | | |
| Only in trial data | 0 | 0 | 0 | 14 | 19 | 33 | 17 | 8 | 25 | 0 | 0 | 0 |
| Only in RCD | 0 | 0 | 0 | 194 | 275 | 469 | 208 | 491 | 699 | 0 | 0 | 0 |
| In both datasets | 0 | 0 | 0 | 43 | 48 | 91 | 312 | 308 | 620 | 0 | 0 | 0 |
| **Time difference when event present in both datasets** | | | | | | **No. (%)** | | | | | | |
| <6 months | 211 (62.1%) | 146 (44.5%) | 357 (53.4%) | 178 (78.4%) | 111 (60.0%) | 289 (70.1%) | 57 (87.7%) | 27 (100%) | 84 (91.3%) | 241 (71.3%) | 157 (48.0%) | 398 (59.8%) |
| 6-12 months | 23 (6.8%) | 32 (9.8%) | 55 (8.2%) | 12 (5.3%) | 17 (9.2%) | 29 (7.0%) | 3 (4.6%) | 0 (0.0%) | 3 (3.3%) | 19 (5.6%) | 34 (10.4%) | 53 (8.0%) |
| >1 year | 106 (31.2%) | 150 (45.7%) | 256 (38.3%) | 37 (16.3%) | 57 (30.8%) | 94 (22.8%) | 5 (7.7%) | 0 (0.0%) | 5 (5.4%) | 78 (23.1%) | 136 (41.6%) | 214 (32.2%) |
| **Performance measures[c]** | | | | | | **% (95% CI)** | | | | | | |
| *All time periods* | | | | | | | | | | | | |
| Sensitivity | 98.3 (96.9, 99.6) | 97.6 (96.0, 99.2) | 97.9 (96.9, 99.0) | 97.4 (95.4, 99.5) | 96.4 (93.7, 99.0) | 96.9 (95.3, 98.6) | 94.2 (88.7, 99.7) | 87.1 (75.3, 98.9) | 92.0 (86.7, 97.3) | 97.7 (96.1, 99.3) | 97.3 (95.6, 99.0) | 97.5 (96.3, 98.7) |
| Specificity | 67.5 (64.0, 71.0) | 33.3 (29.8, 36.8) | 50.3 (47.7, 52.9) | 81.5 (78.3, 84.7) | 43.4 (39.0, 47.7) | 63.4 (60.5, 66.3) | 93.6 (91.3, 95.9) | 93.0 (89.5, 96.6) | 93.4 (91.5, 95.3) | 72.7 (69.3, 76.0) | 35.8 (32.3, 39.4) | 54.1 (51.5, 56.8) |
| PPV | 60.1 (56.0, 64.1) | 41.2 (37.7, 44.6) | 49.0 (46.4, 51.7) | 68.8 (63.8, 73.8) | 39.3 (34.9, 43.7) | 51.4 (48.0, 54.9) | 69.9 (60.6, 79.2) | 65.9 (51.3, 80.4) | 68.7 (60.8, 76.5) | 64.0 (59.9, 68.1) | 42.0 (38.6, 45.5) | 50.9 (48.2, 53.6) |
| NPV | 98.7 (97.7, 99.7) | 96.7 (94.4, 98.9) | 98.0 (97.0, 99.1) | 98.7 (97.7, 99.7) | 96.9 (94.6, 99.2) | 98.1 (97.1, 99.1) | 99.0 (98.1, 100) | 97.9 (95.9, 99.9) | 98.7 (97.8, 99.6) | 98.4 (97.4, 99.5) | 96.6 (94.3, 98.8) | 97.8 (96.8, 98.8) |
| *Within 6 months of trial data* | | | | | | | | | | | | |
| Sensitivity | 61.0 (55.8, 66.1) | 43.5 (38.2, 48.8) | 52.3 (48.6, 56.1) | 76.4 (70.9, 81.8) | 57.8 (50.8, 64.8) | 68.0 (63.6, 72.4) | 82.6 (73.7, 91.6) | 87.1 (75.3, 98.9) | 84.0 (76.8, 91.2) | 69.7 (64.8, 74.5) | 46.7 (41.4, 52.1) | 58.4 (54.7, 62.1) |
| Specificity | 67.5 (64.0, 71.0) | 33.3 (29.8, 36.8) | 50.3 (47.7, 52.9) | 81.5 (78.3, 84.7) | 43.4 (39.0, 47.7) | 63.4 (60.5, 66.3) | 93.6 (91.3, 95.9) | 93.0 (89.5, 96.6) | 93.4 (91.5, 95.3) | 72.7 (69.3, 76.0) | 35.8 (32.3, 39.4) | 54.1 (51.5, 56.8) |
| PPV | 48.3 (43.6, 53.0) | 23.7 (20.4, 27.1) | 33.9 (31.1, 36.8) | 63.3 (57.7, 69.0) | 28.0 (23.5, 32.4) | 42.6 (38.9, 46.3) | 67.1 (57.1, 77.1) | 65.9 (51.3, 80.4) | 66.7 (58.4, 74.9) | 55.9 (51.2, 60.6) | 25.8 (22.3, 29.3) | 38.3 (35.4, 41.3) |
| NPV | 77.6 (74.3, 81.0) | 55.2 (50.5, 59.9) | 68.4 (65.5, 71.2) | 89.2 (86.5, 91.9) | 73.0 (68.0, 78.0) | 83.2 (80.6, 85.8) | 97.1 (95.5, 98.7) | 97.9 (95.9, 99.9) | 97.4 (96.1, 98.6) | 82.8 (79.8, 85.8) | 58.5 (53.8, 63.1) | 72.7 (70.0, 75.4) |

PPV, Positive predictive value; NPV, Negative predictive value. [a] Analysis period starts at 1 or 5 years after randomisation. [b] Post-validation adjustment ignores events reported in the RCD as locoregional recurrence, recurrence of unknown type or contralateral breast cancer during the first year after diagnosis. [c] Performance measures defined in footnote of Table 3

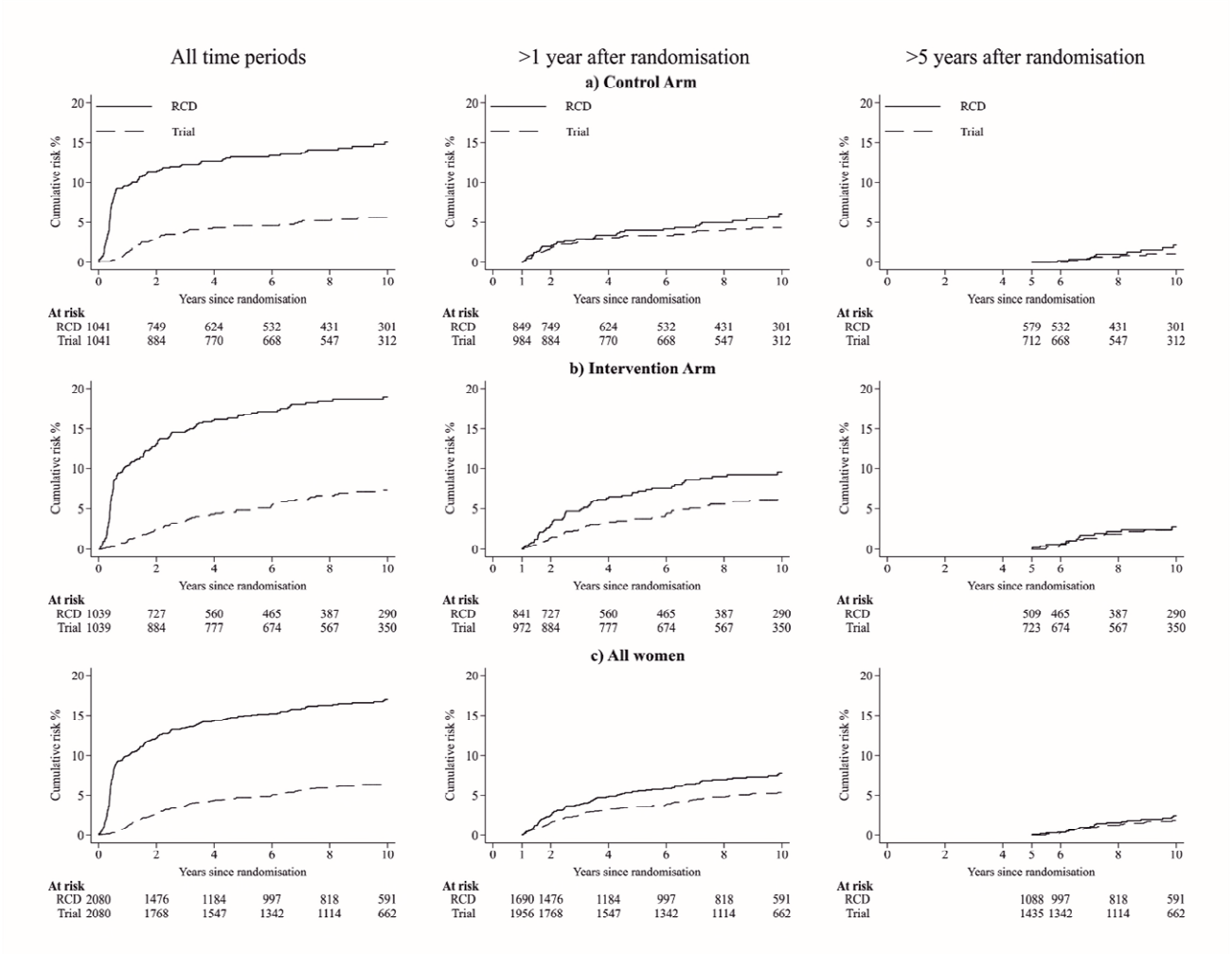


**Figure S4. External validation exercise: Cumulative risk of locoregional recurrence in AZURE trial (dashed lines) and in routinely collected data (RCD) (solid lines). Analyses are by separate randomisation arm (a and b), and for all 2080 women included in external validation group (c).** The outcome of locoregional recurrence is defined in Table S4. Plotted values at 1-, 3-, 5- and 10-years (and 95% confidence intervals) are in Table S9.

**Table S9. External Validation exercise: Number of events and cumulative risks of locoregional recurrence by time since randomisation and AZURE trial arm, for routinely collected data (RCD) and AZURE trial data.** Calculated for all 2080 women in the external validation cohort.

| | | | All time periods | | | >1 year after randomisation | | | >5 years after randomisation | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Trial Arm** | **Dataset** | **Time since randomisation (years)** | **No. women at risk[a]** | **No. events[b]** | **Cumulative risk[c] % (95% CI)** | **No. women at risk[a]** | **No. events[b]** | **Cumulative risk[c] % (95% CI)** | **No. women at risk[a]** | **No. events[b]** | **Cumulative risk[c] % (95% CI)** |
| **Control** | RCD | 0-1 | 1041 | 94 | 9.5 (7.8, 11.5) | - | - | - | - | - | - |
| | | 1-3 | 849 | 23 | 12.2 (10.3, 14.4) | 849 | 23 | 3.0 (2.0, 4.5) | - | - | - |
| | | 3-5 | 668 | 7 | 13.2 (11.1, 15.5) | 668 | 7 | 4.1 (2.9, 5.8) | - | - | - |
| | | 5-10 | 579 | 9 | 14.9 (12.7, 17.5) | 579 | 9 | 6.0 (4.4, 8.2) | 579 | 9 | 2.0 (1.1, 3.9) |
| | Trial | 0-1 | 1041 | 13 | 1.3 (0.7, 2.2) | - | - | - | - | - | - |
| | | 1-3 | 984 | 24 | 3.9 (2.8, 5.3) | 984 | 24 | 2.6 (1.8, 3.9) | - | - | - |
| | | 3-5 | 817 | 6 | 4.6 (3.4, 6.2) | 817 | 6 | 3.4 (2.4, 4.8) | - | - | - |
| | | 5-10 | 712 | 6 | 5.7 (4.3, 7.6) | 712 | 6 | 4.5 (3.2, 6.3) | 712 | 6 | 1.2 (0.5, 2.6) |
| **Intervention** | RCD | 0-1 | 1039 | 102 | 10.3 (8.6, 12.4) | | | | - | - | - |
| | | 1-3 | 841 | 36 | 14.6 (12.5, 17.0) | 841 | 36 | 4.8 (3.5, 6.6) | - | - | - |
| | | 3-5 | 625 | 14 | 16.7 (14.4, 19.3) | 625 | 14 | 7.1 (5.4, 9.3) | - | - | - |
| | | 5-10 | 509 | 12 | 19.1 (16.6, 22.1) | 509 | 12 | 9.9 (7.7, 12.6) | 509 | 12 | 3.0 (1.7, 5.2) |
| | Trial | 0-1 | 1039 | 11 | 1.1 (0.6, 2.0) | - | - | - | - | - | - |
| | | 1-3 | 972 | 22 | 3.5 (2.5, 4.9) | 972 | 22 | 2.4 (1.6, 3.7) | - | - | - |
| | | 3-5 | 825 | 11 | 4.8 (3.6, 6.5) | 825 | 11 | 3.8 (2.7, 5.3) | - | - | - |
| | | 5-10 | 723 | 16 | 7.6 (5.9, 9.8) | 723 | 16 | 6.6 (5.0, 8.7) | 723 | 16 | 2.9 (1.8, 4.8) |
| **Total** | RCD | 0-1 | 2080 | 196 | 9.9 (8.6, 11.3) | - | - | - | - | - | - |
| | | 1-3 | 1690 | 59 | 13.4 (11.9, 15.0) | 1690 | 59 | 3.9 (3.0, 5.0) | - | - | - |
| | | 3-5 | 1293 | 21 | 14.9 (13.3, 16.6) | 1293 | 21 | 5.6 (4.5, 6.9) | - | - | - |
| | | 5-10 | 1088 | 21 | 17.0 (15.3, 18.9) | 1088 | 21 | 7.9 (6.5, 9.6) | 1088 | 21 | 2.5 (1.6, 3.8) |
| | Trial | 0-1 | 2080 | 24 | 1.2 (0.8, 1.8) | - | - | - | - | - | - |
| | | 1-3 | 1956 | 46 | 3.7 (2.9, 4.6) | 1956 | 46 | 2.5 (1.9, 3.4) | - | - | - |
| | | 3-5 | 1642 | 17 | 4.7 (3.9, 5.8) | 1642 | 17 | 3.6 (2.8, 4.6) | - | - | - |
| | | 5-10 | 1435 | 22 | 6.7 (5.6, 8.1) | 1435 | 22 | 5.6 (4.5, 6.9) | 1435 | 22 | 2.1 (1.4, 3.1) |

[a] Number of women at risk at start of time category
[b] Number of events during time category
[c] Cumulative risk at end of time category

**Table S10. External validation exercise: Agreement of routinely collected data (RCD) and AZURE trial data for locoregional recurrence.**
Calculations performed for all 2080 women in external validation cohort.

| Locoregional recurrence[a] | Analysis period and trial arm | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | All time periods | | | >1 year after randomisation[b] | | | >5 years after randomisation[b] | | |
| | Control (N=1041) | Intervention (N=1039) | Total (N=2080) | Control (N=1041) | Intervention (N=1039) | Total (N=2080) | Control (N=1041) | Intervention (N=1039) | Total (N=2080) |
| | | | | | No. | | | | |
| Event in both datasets | 23 | 31 | 54 | 16 | 21 | 37 | 2 | 4 | 6 |
| Event only in trial data | 26 | 29 | 55 | 15 | 19 | 34 | 3 | 3 | 6 |
| Event only in RCD | 110 | 133 | 243 | 22 | 39 | 61 | 6 | 8 | 14 |
| No event in either dataset | 882 | 846 | 1728 | 780 | 740 | 1520 | 545 | 477 | 1022 |
| **Censored before analysis period** | | | | | | | | | |
| Only in trial data | 0 | 0 | 0 | 16 | 22 | 38 | 23 | 17 | 40 |
| Only in RCD | 0 | 0 | 0 | 151 | 153 | 304 | 156 | 231 | 387 |
| In both datasets | 0 | 0 | 0 | 41 | 45 | 86 | 306 | 299 | 605 |
| **Time difference when event present in both datasets** | | | | | No. (%) | | | | |
| <6 months | 15 (65.2%) | 24 (77.4%) | 39 (72.2%) | 13 (81.2%) | 19 (90.5%) | 32 (86.5%) | 2 (100%) | 4 (100%) | 6 (100%) |
| 6-12 months | 5 (21.7%) | 0 (0.0%) | 5 (9.3%) | 2 (12.5%) | 0 (0.0%) | 2 (5.4%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| >1 year | 3 (13.0%) | 7 (22.6%) | 10 (18.5%) | 1 (6.2%) | 2 (9.5%) | 3 (8.1%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| **Performance measures[c]** | | | | | % (95% CI) | | | | |
| *All time periods* | | | | | | | | | |
| Sensitivity | 46.9 (33.0, 60.9) | 51.7 (39.0, 64.3) | 49.5 (40.2, 58.9) | 51.6 (34.0, 69.2) | 52.5 (37.0, 68.0) | 52.1 (40.5, 63.7) | 40.0 (0.0, 82.9) | 57.1 (20.5, 93.8) | 50.0 (21.7, 78.3) |
| Specificity | 88.9 (87.0, 90.9) | 86.4 (84.3, 88.6) | 87.7 (86.2, 89.1) | 97.3 (96.1, 98.4) | 95.0 (93.5, 96.5) | 96.1 (95.2, 97.1) | 98.9 (98.0, 99.8) | 98.4 (97.2, 99.5) | 98.6 (97.9, 99.4) |
| PPV | 17.3 (10.9, 23.7) | 18.9 (12.9, 24.9) | 18.2 (13.8, 22.6) | 42.1 (26.4, 57.8) | 35.0 (22.9, 47.1) | 37.8 (28.2, 47.4) | 25.0 (0.0, 55.0) | 33.3 (6.7, 60.0) | 30.0 (9.9, 50.1) |
| NPV | 97.1 (96.1, 98.2) | 96.7 (95.5, 97.9) | 96.9 (96.1, 97.7) | 98.1 (97.2, 99.1) | 97.5 (96.4, 98.6) | 97.8 (97.1, 98.5) | 99.5 (98.8, 100) | 99.4 (98.7, 100) | 99.4 (99.0, 99.9) |
| *Within 6 months of trial data* | | | | | | | | | |
| Sensitivity | 30.6 (17.7, 43.5) | 40.0 (27.6, 52.4) | 35.8 (26.8, 44.8) | 41.9 (24.6, 59.3) | 47.5 (32.0, 63.0) | 45.1 (33.5, 56.6) | 40.0 (0.0, 82.9) | 57.1 (20.5, 93.8) | 50.0 (21.7, 78.3) |
| Specificity | 88.9 (87.0, 90.9) | 86.4 (84.3, 88.6) | 87.7 (86.2, 89.1) | 97.3 (96.1, 98.4) | 95.0 (93.5, 96.5) | 96.1 (95.2, 97.1) | 98.9 (98.0, 99.8) | 98.4 (97.2, 99.5) | 98.6 (97.9, 99.4) |
| PPV | 12.0 (6.3, 17.7) | 15.3 (9.7, 20.9) | 13.8 (9.8, 17.9) | 37.1 (21.1, 53.2) | 32.8 (20.7, 44.8) | 34.4 (24.8, 44.1) | 25.0 (0.0, 55.0) | 33.3 (6.7, 60.0) | 30.0 (9.9, 50.1) |
| NPV | 96.3 (95.1, 97.5) | 95.9 (94.6, 97.2) | 96.1 (95.2, 97.0) | 97.7 (96.7, 98.8) | 97.2 (96.1, 98.4) | 97.5 (96.7, 98.3) | 99.5 (98.8, 100) | 99.4 (98.7, 100) | 99.4 (99.0, 99.9) |

PPV, Positive predictive value; NPV, Negative predictive value

[a] Women are censored at contralateral breast cancer, distant metastases, non-breast cancer malignancies and death (Table S4)

[b] Analysis period starts at 1 or 5 years after randomisation

[c] Performance measures defined in footnote of Table 3

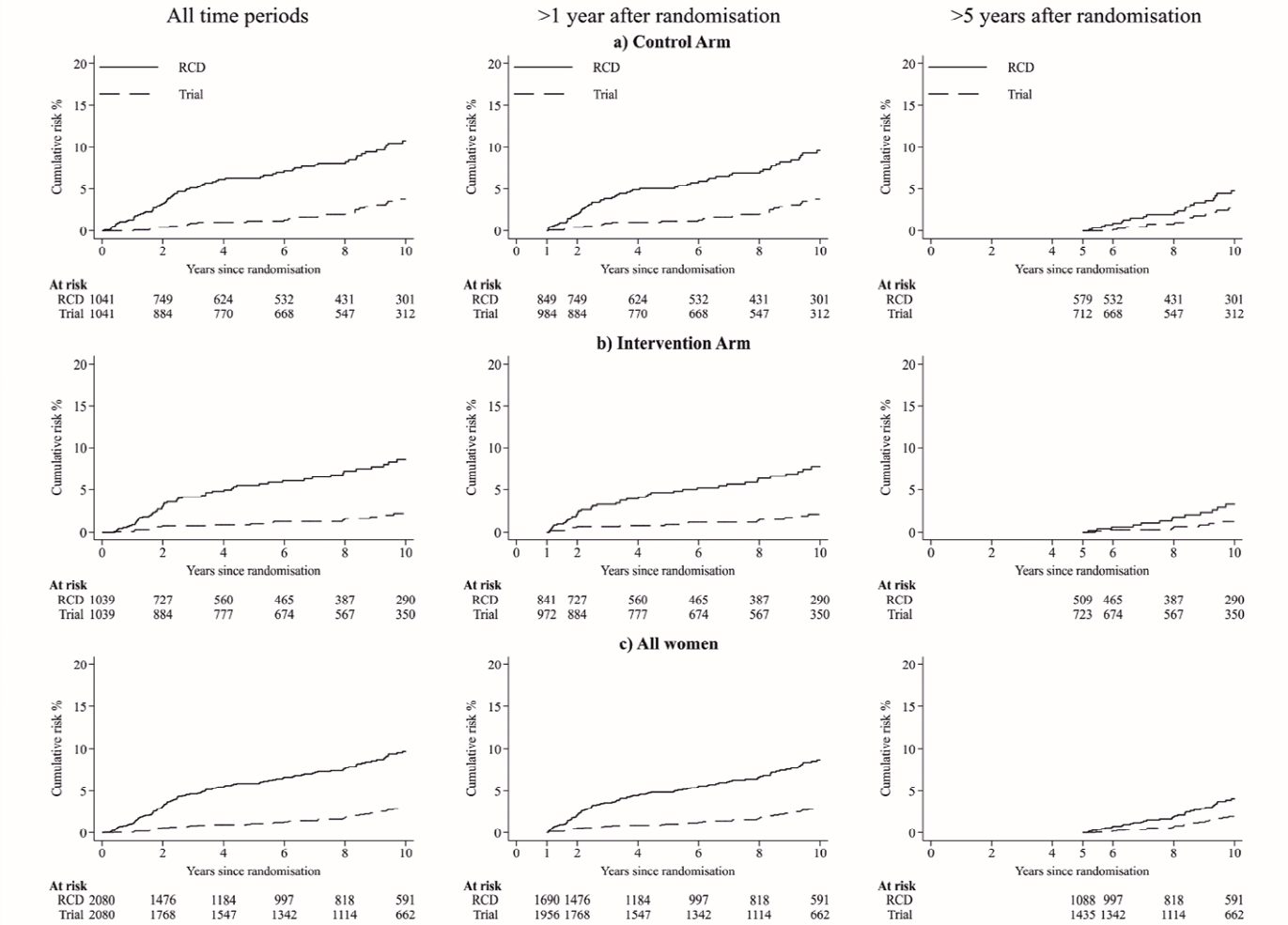


**Figure S5. External validation exercise: Cumulative risk of contralateral breast cancer in AZURE trial (dashed lines) and in routinely collected data (RCD) (solid lines). Analyses are by separate randomisation arm (a and b), and for all 2080 women included in external validation group (c).** The outcome of contralateral breast cancer is defined in Table S4. Plotted values at 1-, 3-, 5- and 10-years (and 95% confidence intervals) are in Table S11.

**Table S11. External validation exercise: Number of events and cumulative risks of contralateral breast cancer by time since randomisation and AZURE trial arm, for routinely collected data (RCD) and trial data.** Calculated for all 2080 women in the external validation cohort.

| | | | All time periods | | | >1 year after randomisation | | | >5 years after randomisation | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Trial Arm** | **Dataset** | **Time since randomisation (years)** | **No. women at risk[a]** | **No. events[b]** | **Cumulative risk[c] % (95% CI)** | **No. women at risk[a]** | **No. events[b]** | **Cumulative risk[c] % (95% CI)** | **No. women at risk[a]** | **No. events[b]** | **Cumulative risk[c] % (95% CI)** |
| **Control** | RCD | 0-1 | 1041 | 12 | 1.3 (0.7, 2.2) | - | - | - | - | - | - |
| | | 1-3 | 849 | 30 | 5.1 (3.8, 6.8) | 849 | 30 | 3.9 (2.7, 5.5) | - | - | - |
| | | 3-5 | 668 | 8 | 6.3 (4.8, 8.2) | 668 | 8 | 5.1 (3.7, 7.0) | - | - | - |
| | | 5-10 | 579 | 21 | 10.7 (8.5, 13.4) | 579 | 21 | 9.5 (7.4, 12.2) | 579 | 21 | 4.7 (3.1, 7.1) |
| | Trial | 0-1 | 1041 | 0 | 0.0 (NA[d]) | - | - | - | - | - | - |
| | | 1-3 | 984 | 8 | 0.9 (0.4, 1.8) | 984 | 8 | 0.9 (0.4, 1.8) | - | - | - |
| | | 3-5 | 817 | 2 | 1.1 (0.6, 2.1) | 817 | 2 | 1.1 (0.6, 2.1) | - | - | - |
| | | 5-10 | 712 | 14 | 3.8 (2.5, 5.7) | 712 | 14 | 3.8 (2.5, 5.7) | 712 | 14 | 2.7 (1.6, 4.5) |
| **Intervention** | RCD | 0-1 | 1039 | 8 | 0.8 (0.4, 1.7) | - | - | - | - | - | - |
| | | 1-3 | 841 | 25 | 4.2 (3.0, 5.8) | 841 | 25 | 3.4 (2.3, 4.9) | - | - | - |
| | | 3-5 | 625 | 8 | 5.5 (4.1, 7.4) | 625 | 8 | 4.7 (3.4, 6.6) | - | - | - |
| | | 5-10 | 509 | 13 | 8.5 (6.5, 11.1) | 509 | 13 | 7.8 (5.8, 10.3) | 509 | 13 | 3.2 (1.9, 5.5) |
| | Trial | 0-1 | 1039 | 1 | 0.1 (0.0, 0.7) | - | - | - | - | - | - |
| | | 1-3 | 972 | 6 | 0.8 (0.4, 1.6) | 972 | 6 | 0.7 (0.3, 1.5) | - | - | - |
| | | 3-5 | 825 | 2 | 1.0 (0.5, 2.0) | 825 | 2 | 0.9 (0.5, 1.8) | - | - | - |
| | | 5-10 | 723 | 7 | 2.3 (1.4, 3.8) | 723 | 7 | 2.2 (1.3, 3.7) | 723 | 7 | 1.3 (0.6, 2.7) |
| **Total** | RCD | 0-1 | 2080 | 20 | 1.1 (0.7, 1.6) | - | - | - | - | - | - |
| | | 1-3 | 1690 | 55 | 4.6 (3.7, 5.8) | 1690 | 55 | 3.6 (2.8, 4.7) | - | - | - |
| | | 3-5 | 1293 | 16 | 5.9 (4.8, 7.2) | 1293 | 16 | 4.9 (3.9, 6.2) | - | - | - |
| | | 5-10 | 1088 | 34 | 9.6 (8.1, 11.5) | 1088 | 34 | 8.7 (7.2, 10.5) | 1088 | 34 | 4.0 (2.9, 5.5) |
| | Trial | 0-1 | 2080 | 1 | 0.0 (0.0, 0.4) | - | - | - | - | - | - |
| | | 1-3 | 1956 | 14 | 0.8 (0.5, 1.4) | 1956 | 14 | 0.8 (0.5, 1.3) | - | - | - |
| | | 3-5 | 1642 | 4 | 1.1 (0.7, 1.7) | 1642 | 4 | 1.0 (0.7, 1.6) | - | - | - |
| | | 5-10 | 1435 | 21 | 3.0 (2.2, 4.2) | 1435 | 21 | 3.0 (2.2, 4.1) | 1435 | 21 | 2.0 (1.3, 3.0) |

[a] Number of women at risk at start of time category [b] Number of events during time category [c] Cumulative risk at end of time category
[d] Unable to calculate confidence interval when no events are observed

**Table S12. External validation exercise: Agreement of routinely collected data (RCD) and AZURE trial data for contralateral breast cancer.** Calculations performed for all 2080 women in external validation cohort.

| Contralateral breast cancer[a] | Analysis period and trial arm | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | All time periods | | | >1 year after randomisation[b] | | | >5 years after randomisation[b] | | |
| | Control (N=1041) | Intervention (N=1039) | Total (N=2080) | Control (N=1041) | Intervention (N=1039) | Total (N=2080) | Control (N=1041) | Intervention (N=1039) | Total (N=2080) |
| | | | | | No. | | | | |
| Event in both datasets | 18 | 11 | 29 | 18 | 10 | 28 | 13 | 4 | 17 |
| Event only in trial data | 6 | 5 | 11 | 3 | 4 | 7 | 1 | 1 | 2 |
| Event only in RCD | 53 | 43 | 96 | 41 | 35 | 76 | 8 | 7 | 15 |
| No event in either dataset | 964 | 980 | 1944 | 771 | 770 | 1541 | 534 | 480 | 1014 |
| **Censored before analysis period** | | | | | | | | | |
| Only in trial data | 0 | 0 | 0 | 16 | 22 | 38 | 23 | 17 | 40 |
| Only in RCD | 0 | 0 | 0 | 151 | 153 | 304 | 156 | 231 | 387 |
| In both datasets | 0 | 0 | 0 | 41 | 45 | 86 | 306 | 299 | 605 |
| **Time difference when event present in both datasets** | | | | | **No. (%)** | | | | |
| <6 months | 18 (100%) | 11 (100%) | 29 (100%) | 18 (100%) | 10 (100%) | 28 (100%) | 13 (100%) | 4 (100%) | 17 (100%) |
| 6-12 months | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| >1 year | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| **Performance measures[c]** | | | | | **% (95% CI)** | | | | |
| *All time periods* | | | | | | | | | |
| Sensitivity | 75.0 (57.7, 92.3) | 68.8 (46.0, 91.5) | 72.5 (58.7, 86.3) | 85.7 (70.7, 100) | 71.4 (47.8, 95.1) | 80.0 (66.7, 93.3) | 92.9 (79.4, 100) | 80.0 (44.9, 100) | 89.5 (75.7, 100) |
| Specificity | 94.8 (93.4, 96.2) | 95.8 (94.6, 97.0) | 95.3 (94.4, 96.2) | 95.0 (93.4, 96.5) | 95.7 (94.2, 97.1) | 95.3 (94.3, 96.3) | 98.5 (97.5, 99.5) | 98.6 (97.5, 99.6) | 98.5 (97.8, 99.3) |
| PPV | 25.4 (15.2, 35.5) | 20.4 (9.6, 31.1) | 23.2 (15.8, 30.6) | 30.5 (18.8, 42.3) | 22.2 (10.1, 34.4) | 26.9 (18.4, 35.4) | 61.9 (41.1, 82.7) | 36.4 (7.9, 64.8) | 53.1 (35.8, 70.4) |
| NPV | 99.4 (98.9, 99.9) | 99.5 (99.0, 99.9) | 99.4 (99.1, 99.8) | 99.6 (99.2, 100) | 99.5 (99.0, 100) | 99.5 (99.2, 99.9) | 99.8 (99.4, 100) | 99.8 (99.4, 100) | 99.8 (99.5, 100) |
| *Within 6 months of trial data* | | | | | | | | | |
| Sensitivity | 75.0 (57.7, 92.3) | 68.8 (46.0, 91.5) | 72.5 (58.7, 86.3) | 85.7 (70.7, 100) | 71.4 (47.8, 95.1) | 80.0 (66.7, 93.3) | 92.9 (79.4, 100) | 80.0 (44.9, 100) | 89.5 (75.7, 100) |
| Specificity | 94.8 (93.4, 96.2) | 95.8 (94.6, 97.0) | 95.3 (94.4, 96.2) | 95.0 (93.4, 96.5) | 95.7 (94.2, 97.1) | 95.3 (94.3, 96.3) | 98.5 (97.5, 99.5) | 98.6 (97.5, 99.6) | 98.5 (97.8, 99.3) |
| PPV | 25.4 (15.2, 35.5) | 20.4 (9.6, 31.1) | 23.2 (15.8, 30.6) | 30.5 (18.8, 42.3) | 22.2 (10.1, 34.4) | 26.9 (18.4, 35.4) | 61.9 (41.1, 82.7) | 36.4 (7.9, 64.8) | 53.1 (35.8, 70.4) |
| NPV | 99.4 (98.9, 99.9) | 99.5 (99.0, 99.9) | 99.4 (99.1, 99.8) | 99.6 (99.2, 100) | 99.5 (99.0, 100) | 99.5 (99.2, 99.9) | 99.8 (99.4, 100) | 99.8 (99.4, 100) | 99.8 (99.5, 100) |

PPV, Positive predictive value; NPV, Negative predictive value

[a] Women are censored at locoregional recurrence, distant metastases, non-breast cancer malignancies and death (Table S4)

[b] Analysis period starts at 1 or 5 years after randomisation

[c] Performance measures defined in footnote of Table 3

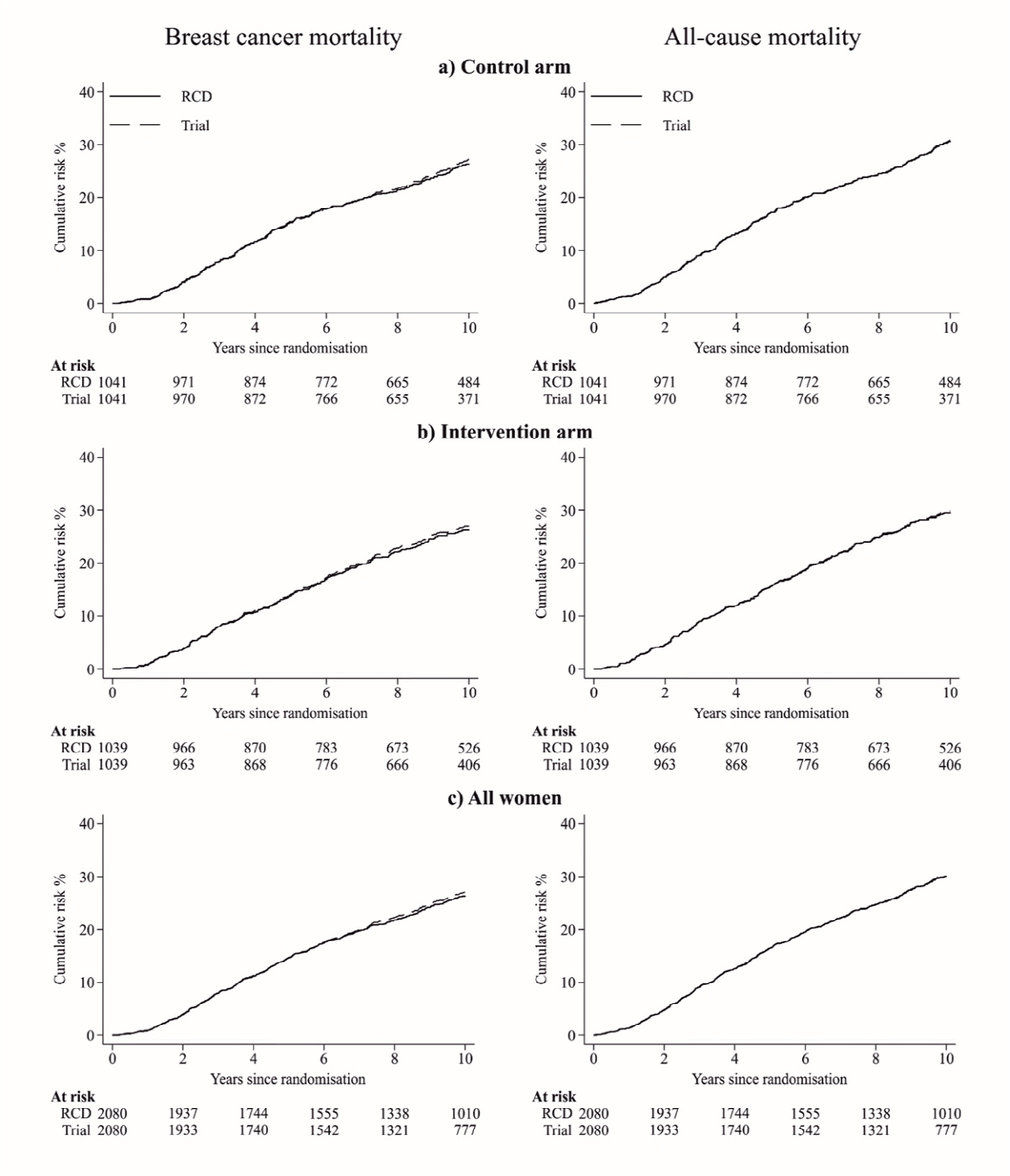


**Figure S6. External validation exercise: Cumulative risk of breast cancer mortality and all-cause mortality in AZURE trial (dashed lines) and in routinely collected data (RCD) (solid lines). Analyses are by separate randomisation arm (a and b), and for all 2080 women included in the external validation group (c).** The outcomes of breast cancer mortality and all-cause mortality are defined in Table S4. Plotted values at 1-, 3-, 5- and 10-years (and 95% confidence intervals) are in Table S13.

**Table S13. External validation exercise: Number of events and cumulative risks of breast cancer mortality and all-cause mortality by time since randomisation and AZURE trial arm, for routinely collected data (RCD) and AZURE trial data.** Calculated for all 2080 women in the external validation cohort.

| Trial Arm | Dataset | Time since randomisation (years) | Breast cancer mortality | | | All-cause mortality | | |
|---|---|---|---|---|---|---|---|---|
| | | | No. women at risk[a] | No. events[b] | Cumulative risk[c] % (95% CI) | No. women at risk[a] | No. events[b] | Cumulative risk[c] % (95% CI) |
| **Control** | RCD | 0-1 | 1041 | 9 | 0.9 (0.5, 1.7) | 1041 | 14 | 1.4 (0.8, 2.3) |
| | | 1-3 | 1019 | 71 | 7.8 (6.4, 9.7) | 1019 | 79 | 9.0 (7.4, 11.0) |
| | | 3-5 | 927 | 75 | 15.4 (13.3, 17.8) | 927 | 82 | 17.2 (15.0, 19.7) |
| | | 5-10 | 821 | 92 | 26.6 (23.8, 29.6) | 821 | 117 | 30.8 (28.0, 33.9) |
| | Trial | 0-1 | 1041 | 8 | 0.8 (0.4, 1.5) | 1041 | 14 | 1.4 (0.8, 2.3) |
| | | 1-3 | 1015 | 73 | 8.0 (6.5, 9.8) | 1015 | 80 | 9.2 (7.6, 11.1) |
| | | 3-5 | 925 | 72 | 15.3 (13.2, 17.7) | 925 | 80 | 17.2 (15.0, 19.6) |
| | | 5-10 | 813 | 99 | 28.4 (25.5, 31.5) | 813 | 117 | 32.1 (29.1, 35.3) |
| **Intervention** | RCD | 0-1 | 1039 | 10 | 1.0 (0.5, 1.8) | 1039 | 14 | 1.4 (0.8, 2.3) |
| | | 1-3 | 1014 | 71 | 8.0 (6.5, 9.9) | 1014 | 78 | 9.0 (7.4, 11.0) |
| | | 3-5 | 914 | 57 | 13.8 (11.8, 16.1) | 914 | 66 | 15.7 (13.6, 18.1) |
| | | 5-10 | 827 | 110 | 26.8 (24.0, 29.8) | 827 | 126 | 30.0 (27.2, 33.1) |
| | Trial | 0-1 | 1039 | 8 | 0.8 (0.4, 1.5) | 1039 | 14 | 1.4 (0.8, 2.3) |
| | | 1-3 | 1012 | 73 | 8.0 (6.5, 9.9) | 1012 | 78 | 9.0 (7.4, 11.0) |
| | | 3-5 | 912 | 59 | 14.1 (12.1, 16.4) | 912 | 66 | 15.7 (13.6, 18.1) |
| | | 5-10 | 826 | 113 | 28.5 (25.6, 31.7) | 826 | 127 | 31.5 (28.5, 34.6) |
| **Total** | RCD | 0-1 | 2080 | 19 | 0.9 (0.6, 1.4) | 2080 | 28 | 1.4 (0.9, 2.0) |
| | | 1-3 | 2033 | 142 | 7.9 (6.8, 9.2) | 2033 | 157 | 9.0 (7.9, 10.4) |
| | | 3-5 | 1841 | 132 | 14.6 (13.2, 16.3) | 1841 | 148 | 16.4 (14.9, 18.1) |
| | | 5-10 | 1648 | 202 | 26.7 (24.7, 28.8) | 1648 | 243 | 30.4 (28.4, 32.6) |
| | Trial | 0-1 | 2080 | 16 | 0.8 (0.5, 1.3) | 2080 | 28 | 1.4 (0.9, 2.0) |
| | | 1-3 | 2027 | 146 | 8.0 (6.9, 9.3) | 2027 | 158 | 9.1 (7.9, 10.4) |
| | | 3-5 | 1837 | 131 | 14.7 (13.2, 16.3) | 1837 | 146 | 16.4 (14.9, 18.1) |
| | | 5-10 | 1639 | 212 | 28.4 (26.4, 30.7) | 1639 | 244 | 31.8 (29.6, 34.0) |

[a] Number of women at risk at the start of the time category
[b] Number of events during time category
[c] Cumulative risk at end of time category

**Table S14. External validation exercise: Agreement of routinely collected data (RCD) and AZURE trial data for breast cancer mortality and all-cause mortality, by AZURE trial arm.** Calculations performed for all 2080 women in external validation cohort.

| | Outcome and trial arm | | | | | |
|---|---|---|---|---|---|---|
| | Breast cancer mortality[a] | | | All-cause mortality | | |
| | Control (N=1041) | Intervention (N=1039) | Total (N=2080) | Control (N=1041) | Intervention (N=1039) | Total (N=2080) |
| | | | No. | | | |
| Event in both datasets | 242 | 247 | 489 | 299 | 289 | 588 |
| Event only in trial data | 17 | 8 | 25 | 0 | 1 | 1 |
| Event only in RCD | 11 | 4 | 15 | 1 | 1 | 2 |
| No event in either dataset | 771 | 780 | 1551 | 741 | 748 | 1489 |
| **Time difference when event present in both datasets** | | | **No. (%)** | | | |
| <6 months | 242 (100%) | 246 (99.6%) | 488 (99.8%) | 299 (100%) | 288 (99.7%) | 587 (99.8%) |
| 6-12 months | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| >1 year | 0 (0.0%) | 1 (0.4%) | 1 (0.2%) | 0 (0.0%) | 1 (0.3%) | 1 (0.2%) |
| **Performance measures[b]** | | | **% (95% CI)** | | | |
| *All time periods* | | | | | | |
| Sensitivity | 93.4 (90.4, 96.5) | 96.9 (94.7, 99.0) | 95.1 (93.3, 97.0) | 100 (100, 100) | 99.7 (99.0, 100) | 99.8 (99.5, 100) |
| Specificity | 98.6 (97.8, 99.4) | 99.5 (99.0, 100) | 99.0 (98.6, 99.5) | 99.9 (99.6, 100) | 99.9 (99.6, 100) | 99.9 (99.7, 100) |
| PPV | 95.7 (93.1, 98.2) | 98.4 (96.9, 100) | 97.0 (95.5, 98.5) | 99.7 (99.0, 100) | 99.7 (99.0, 100) | 99.7 (99.2, 100) |
| NPV | 97.8 (96.8, 98.9) | 99.0 (98.3, 99.7) | 98.4 (97.8, 99.0) | 100 (100, 100) | 99.9 (99.6, 100) | 99.9 (99.8, 100) |
| *Within 6 months of trial data* | | | | | | |
| Sensitivity | 93.4 (90.4, 96.5) | 96.5 (94.2, 98.7) | 94.9 (93.0, 96.8) | 100 (100, 100) | 99.3 (98.4, 100) | 99.7 (99.2, 100) |
| Specificity | 98.6 (97.8, 99.4) | 99.5 (99.0, 100) | 99.0 (98.6, 99.5) | 99.9 (99.6, 100) | 99.9 (99.6, 100) | 99.9 (99.7, 100) |
| PPV | 95.7 (93.1, 98.2) | 98.4 (96.8, 100) | 97.0 (95.5, 98.5) | 99.7 (99.0, 100) | 99.7 (99.0, 100) | 99.7 (99.2, 100) |
| NPV | 97.8 (96.8, 98.9) | 98.9 (98.1, 99.6) | 98.4 (97.7, 99.0) | 100 (100, 100) | 99.7 (99.4, 100) | 99.9 (99.7, 100) |

PPV, Positive predictive value; NPV, Negative predictive value

[a] Women are censored at non-breast-cancer deaths (Table S4)

[b] Performance measures defined in footnote of Table 3

**Table S15a. Training exercise after initial development of algorithm using WMCIU database: Comparison of first outcome events identified by algorithm using routinely collected data (RCD) with first events recorded in the AZURE training sample of 150 women, by trial arm.**

| AZURE | Algorithm based on routinely collected data | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Loco-regional recurrence** | **Distant recurrence** | **Recurrence, type unknown** | **Contra-lateral breast cancer** | **Death from breast cancer** | **Non-breast cancer malignancy** | **Non-breast-cancer death** | **No event recorded** | **Total** |
| a) **Control arm** | | | | | | | | | |
| Locoregional recurrence | **3** | 3 | **2** | 0 | 0 | 0 | 0 | 0 | 8 |
| Distant recurrence | 2 | **16** | **9** | 2 | 2 | 0 | 0 | 0 | 31 |
| Contralateral breast cancer | 1 | 1 | 0 | **0** | 0 | 0 | 0 | 0 | 2 |
| Death from breast cancer | 0 | 0 | 0 | 0 | **0** | 0 | 0 | 0 | 0 |
| Non-breast cancer malignancy | 0 | 1 | 0 | 0 | 0 | **3** | 0 | 0 | 4 |
| Non-breast-cancer death | 0 | 0 | 0 | 0 | 0 | 0 | **3** | 0 | 3 |
| No event recorded | 3 | 5 | 8 | 1 | 0 | 0 | 0 | **0** | 17 |
| Total | 9 | 26 | 19 | 3 | 2 | 3 | 3 | 0 | 65 |
| b) **Intervention arm** | | | | | | | | | |
| Locoregional recurrence | **8** | 3 | **2** | 0 | 0 | 0 | 0 | 0 | 13 |
| Distant recurrence | 5 | **13** | **10** | 1 | 2 | 0 | 1 | 0 | 32 |
| Contralateral breast cancer | 0 | 0 | 1 | **3** | 0 | 0 | 0 | 0 | 4 |
| Death from breast cancer | 0 | 0 | 0 | 0 | **0** | 0 | 0 | 0 | 0 |
| Non-breast cancer malignancy | 1 | 0 | 0 | 0 | 0 | **1** | 0 | 0 | 2 |
| Non-breast-cancer death | 0 | 0 | 0 | 0 | 0 | 1 | **0** | 0 | 1 |
| No event recorded | 3 | 3 | 27 | 0 | 0 | 0 | 0 | **0** | 33 |
| Total | 17 | 19 | 40 | 4 | 2 | 2 | 1 | 0 | 85 |
| c) **All women** | | | | | | | | | |
| Locoregional recurrence | **11** | 6 | **4** | 0 | 0 | 0 | 0 | 0 | 21 |
| Distant recurrence | 7 | **29** | **19** | 3 | 4 | 0 | 1 | 0 | 63 |
| Contralateral breast cancer | 1 | 1 | 1 | **3** | 0 | 0 | 0 | 0 | 6 |
| Death from breast cancer | 0 | 0 | 0 | 0 | **0** | 0 | 0 | 0 | 0 |
| Non-breast cancer malignancy | 1 | 1 | 0 | 0 | 0 | **4** | 0 | 0 | 6 |
| Non-breast-cancer death | 0 | 0 | 0 | 0 | 0 | 1 | **3** | 0 | 4 |
| No event recorded | 6 | 8 | 35 | 1 | 0 | 0 | 0 | **0** | 50 |
| Total | 26 | 45 | 59 | 7 | 4 | 5 | 4 | 0 | 150 |

Entries in the table in bold type and with shading indicate that the outcome using the algorithm based on the RCD and the outcome based on the AZURE Training Sample were judged to be in agreement.

**Table S15b. Training exercise after further training using 150 women from AZURE trial: Comparison of first outcome events identified by algorithm using routinely collected data (RCD) with first events recorded in the AZURE training sample of 150 women, by trial arm.**

| AZURE | Algorithm based on routinely collected data | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Loco-regional recurrence** | **Distant recurrence** | **Recurrence, type unknown** | **Contra-lateral breast cancer** | **Death from breast cancer** | **Non-breast cancer malignancy** | **Non-breast-cancer death** | **No event recorded** | **Total** |
| a) **Control arm** | | | | | | | | | |
| Locoregional recurrence | **3** | 3 | **2** | 0 | 0 | 0 | 0 | 0 | 8 |
| Distant recurrence | 3 | **20** | **6** | 1 | 2 | 0 | 0 | 0 | 31 |
| Contralateral breast cancer | 1 | 1 | 0 | **0** | 0 | 0 | 0 | 0 | 2 |
| Death from breast cancer | 0 | 0 | 0 | 0 | **0** | 0 | 0 | 0 | 0 |
| Non-breast cancer malignancy | 0 | 1 | 0 | 0 | 0 | **3** | 0 | 0 | 4 |
| Non-breast-cancer death | 0 | 0 | 0 | 0 | 0 | 0 | **3** | 0 | 3 |
| No event recorded | 1 | 0 | 2 | 1 | 0 | 0 | 0 | **13** | 17 |
| Total | 7 | 25 | 10 | 2 | 2 | 3 | 3 | 13 | 65 |
| b) **Intervention arm** | | | | | | | | | |
| Locoregional recurrence | **7** | 2 | **2** | 2 | 0 | 0 | 0 | 0 | 13 |
| Distant recurrence | 5 | **16** | **4** | 3 | 4 | 0 | 0 | 0 | 32 |
| Contralateral breast cancer | 0 | 0 | 0 | **4** | 0 | 0 | 0 | 0 | 4 |
| Death from breast cancer | 0 | 0 | 0 | 0 | **0** | 0 | 0 | 0 | 0 |
| Non-breast cancer malignancy | 1 | 0 | 0 | 0 | 0 | **1** | 0 | 0 | 2 |
| Non-breast-cancer death | 0 | 0 | 0 | 0 | 0 | 1 | **0** | 0 | 1 |
| No event recorded | 2 | 2 | 2 | 0 | 0 | 0 | 0 | **27** | 33 |
| Total | 15 | 20 | 8 | 9 | 4 | 2 | 0 | 27 | 85 |
| c) **All women** | | | | | | | | | |
| Locoregional recurrence | **10** | 5 | **4** | 2 | 0 | 0 | 0 | 0 | 21 |
| Distant recurrence | 7 | **36** | **10** | 4 | 6 | 0 | 0 | 0 | 63 |
| Contralateral breast cancer | 1 | 1 | 0 | **4** | 0 | 0 | 0 | 0 | 6 |
| Death from breast cancer | 0 | 0 | 0 | 0 | **0** | 0 | 0 | 0 | 0 |
| Non-breast cancer malignancy | 1 | 1 | 0 | 0 | 0 | **4** | 0 | 0 | 6 |
| Non-breast-cancer death | 0 | 0 | 0 | 0 | 0 | 1 | **3** | 0 | 4 |
| No event recorded | 3 | 2 | 4 | 1 | 0 | 0 | 0 | **40** | 50 |
| Total | 22 | 45 | 18 | 11 | 6 | 5 | 3 | 40 | 150 |

Entries in the table in bold type and with shading indicate that the outcome using the algorithm based on the RCD and the outcome based on the AZURE Training Sample were judged to be in agreement.

**Table S16. Internal validation exercise: Comparison of first outcome events identified by algorithm using routinely collected data (RCD) with first events recorded in the AZURE trial, for women in the control arm (a), intervention arm (b), and for all women in the internal validation group (c).**

| AZURE | Algorithm based on routinely collected data | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | Locoregional recurrence | Distant recurrence | Recurrence, type unknown | Contralateral breast cancer | Death from breast cancer | Non-breast cancer malignancy | Non-breast-cancer death | No event recorded | |
| a) **Control arm** | | | | | | | | | |
| Locoregional recurrence | **17** | 7 | **6** | 5 | 2 | 1 | 0 | 3 | 41 |
| Distant recurrence | 29 | **157** | **26** | 11 | 8 | 0 | 0 | 4 | 235 |
| Contralateral breast cancer | 3 | 0 | 0 | **18** | 0 | 0 | 0 | 1 | 22 |
| Death from breast cancer | 1 | 4 | 0 | 0 | **1** | 0 | 1 | 0 | 7 |
| Non-breast cancer malignancy | 2 | 7 | 0 | 0 | 0 | **25** | 0 | 7 | 41 |
| Non-breast-cancer death | 0 | 1 | 0 | 1 | 2 | 0 | **12** | 0 | 16 |
| No event recorded | 34 | 18 | 16 | 18 | 0 | 5 | 0 | **523** | 614 |
| Total | 86 | 194 | 48 | 53 | 13 | 31 | 13 | 538 | 976 |
| b) **Intervention arm** | | | | | | | | | |
| Locoregional recurrence | **18** | 13 | **6** | 5 | 1 | 1 | 1 | 2 | 47 |
| Distant recurrence | 27 | **149** | **29** | 1 | 10 | 3 | 1 | 2 | 222 |
| Contralateral breast cancer | 2 | 2 | 0 | **8** | 0 | 0 | 0 | 0 | 12 |
| Death from breast cancer | 0 | 4 | 0 | 0 | **2** | 0 | 0 | 0 | 6 |
| Non-breast cancer malignancy | 3 | 4 | 1 | 1 | 0 | **15** | 0 | 7 | 31 |
| Non-breast-cancer death | 3 | 4 | 2 | 1 | 1 | 0 | **8** | 1 | 20 |
| No event recorded | 59 | 54 | 54 | 13 | 0 | 3 | 0 | **433** | 616 |
| Total | 112 | 230 | 92 | 29 | 14 | 22 | 10 | 445 | 954 |
| c) **Overall** | | | | | | | | | |
| Locoregional recurrence | **35** | 20 | **12** | 10 | 3 | 2 | 1 | 5 | 88 |
| Distant recurrence | 56 | **306** | **55** | 12 | 18 | 3 | 1 | 6 | 457 |
| Contralateral breast cancer | 5 | 2 | 0 | **26** | 0 | 0 | 0 | 1 | 34 |
| Death from breast cancer | 1 | 8 | 0 | 0 | **3** | 0 | 1 | 0 | 13 |
| Non-breast cancer malignancy | 5 | 11 | 1 | 1 | 0 | **40** | 0 | 14 | 72 |
| Non-breast-cancer death | 3 | 5 | 2 | 2 | 3 | 0 | **20** | 1 | 36 |
| No event recorded | 93 | 72 | 70 | 31 | 0 | 8 | 0 | **956** | 1230 |
| Total | 198 | 424 | 140 | 82 | 27 | 53 | 23 | 983 | 1930 |

Entries in the table in bold type and with shading indicate that the outcome using the algorithm based on the RCD and the outcome based on the AZURE Training Sample were judged to be in agreement.

**Table S17. Internal validation exercise: Number of events and cumulative risks of distant recurrence by time since randomisation and AZURE trial arm, for routinely collected data (RCD) and AZURE trial data.** Calculated for all 1930 women in the internal validation group.

| | | | All time periods | | | >5 years after randomisation | | |
|---|---|---|---|---|---|---|---|---|
| **Trial Arm** | **Dataset** | **Time since randomisation (years)** | **No. women at risk[a]** | **No. events[b]** | **Cumulative risk[c] % (95% CI)** | **No. women at risk[a]** | **No. events[b]** | **Cumulative risk[c] % (95% CI)** |
| **Control** | RCD | 0-1 | 976 | 25 | 2.6 (1.7, 3.8) | - | - | - |
| | | 1-3 | 938 | 105 | 13.6 (11.6, 15.9) | - | - | - |
| | | 3-5 | 812 | 58 | 19.9 (17.5, 22.6) | - | - | - |
| | | 5-10 | 728 | 107 | 33.8 (30.7, 37.1) | 728 | 107 | 17.4 (14.6, 20.6) |
| | Trial | 0-1 | 976 | 24 | 2.5 (1.7, 3.7) | - | - | - |
| | | 1-3 | 933 | 111 | 14.2 (12.1, 16.6) | - | - | - |
| | | 3-5 | 803 | 53 | 20.0 (17.6, 22.7) | - | - | - |
| | | 5-10 | 707 | 88 | 32.7 (29.6, 36.1) | 707 | 88 | 15.8 (13.1, 19.2) |
| **Intervention** | RCD | 0-1 | 954 | 26 | 2.7 (1.9, 4.0) | - | - | - |
| | | 1-3 | 911 | 127 | 16.5 (14.3, 19.0) | - | - | - |
| | | 3-5 | 760 | 91 | 26.7 (23.9, 29.7) | - | - | - |
| | | 5-10 | 638 | 85 | 37.9 (34.7, 41.2) | 638 | 85 | 15.2 (12.5, 18.5) |
| | Trial | 0-1 | 954 | 27 | 2.9 (2.0, 4.1) | - | - | - |
| | | 1-3 | 905 | 89 | 12.6 (10.6, 14.9) | - | - | - |
| | | 3-5 | 789 | 57 | 19.0 (16.6, 21.7) | - | - | - |
| | | 5-10 | 700 | 87 | 31.4 (28.3, 34.8) | 700 | 87 | 15.4 (12.6, 18.6) |
| **Total** | RCD | 0-1 | 1930 | 51 | 2.7 (2.0, 3.5) | - | - | - |
| | | 1-3 | 1849 | 232 | 15.0 (13.5, 16.7) | - | - | - |
| | | 3-5 | 1572 | 149 | 23.2 (21.4, 25.2) | - | - | - |
| | | 5-10 | 1366 | 192 | 35.8 (33.6, 38.1) | 1366 | 192 | 16.4 (14.4, 18.6) |
| | Trial | 0-1 | 1930 | 51 | 2.7 (2.0, 3.5) | - | - | - |
| | | 1-3 | 1838 | 200 | 13.4 (11.9, 15.0) | - | - | - |
| | | 3-5 | 1592 | 110 | 19.5 (17.8, 21.4) | - | - | - |
| | | 5-10 | 1407 | 175 | 32.1 (29.8, 34.4) | 1407 | 175 | 15.6 (13.6, 17.9) |

[a] Number of women at risk at start of time category
[b] Number of events during time category
[c] Cumulative risk at end of time category

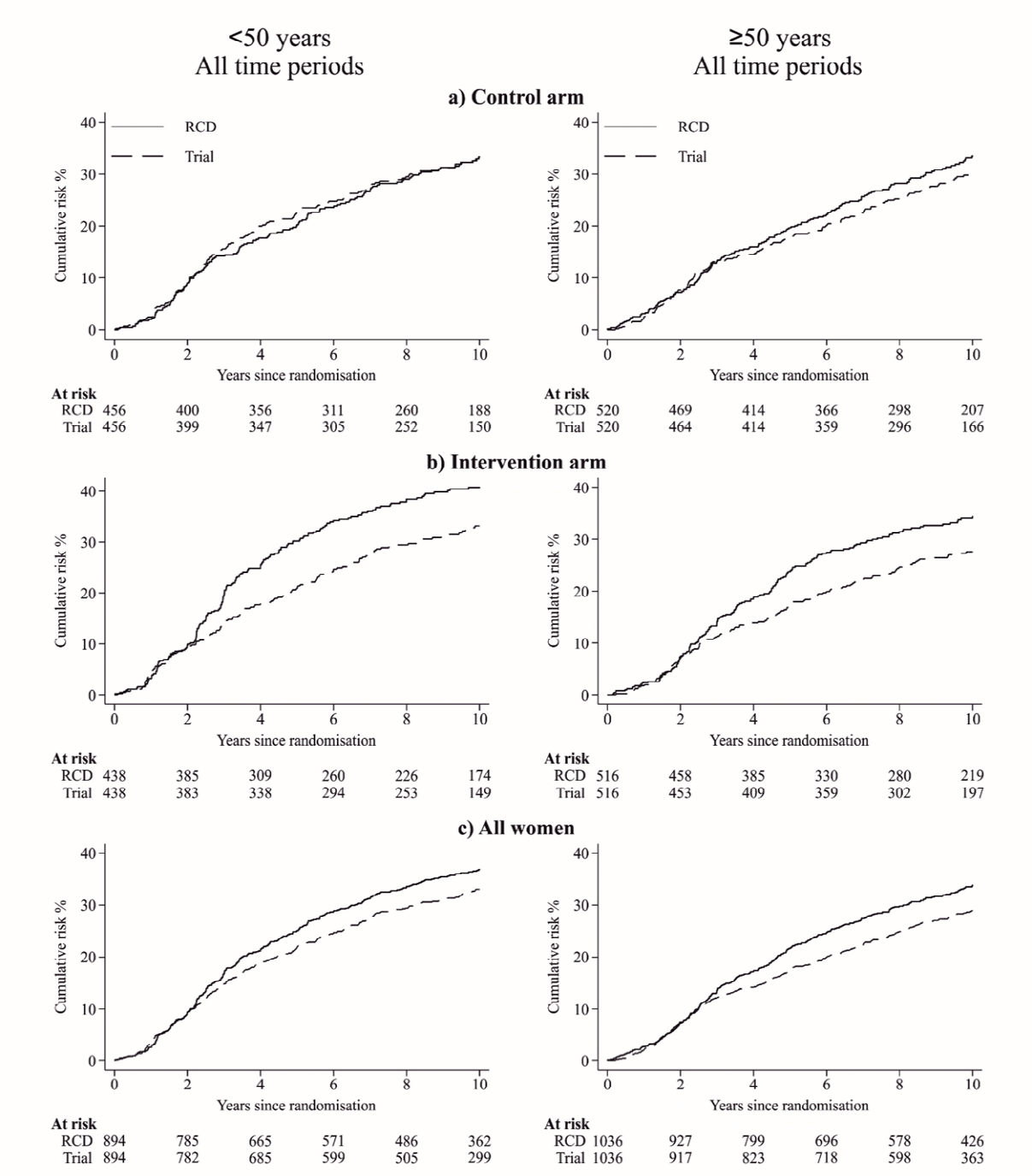


**Figure S7. Internal validation exercise: Cumulative risk of distant recurrence in AZURE trial (dashed lines) and in the routinely collected data (RCD) (solid lines), split by age at randomisation. Analyses are by randomisation arm (a and b), and for all women included in the internal validation group (c).**

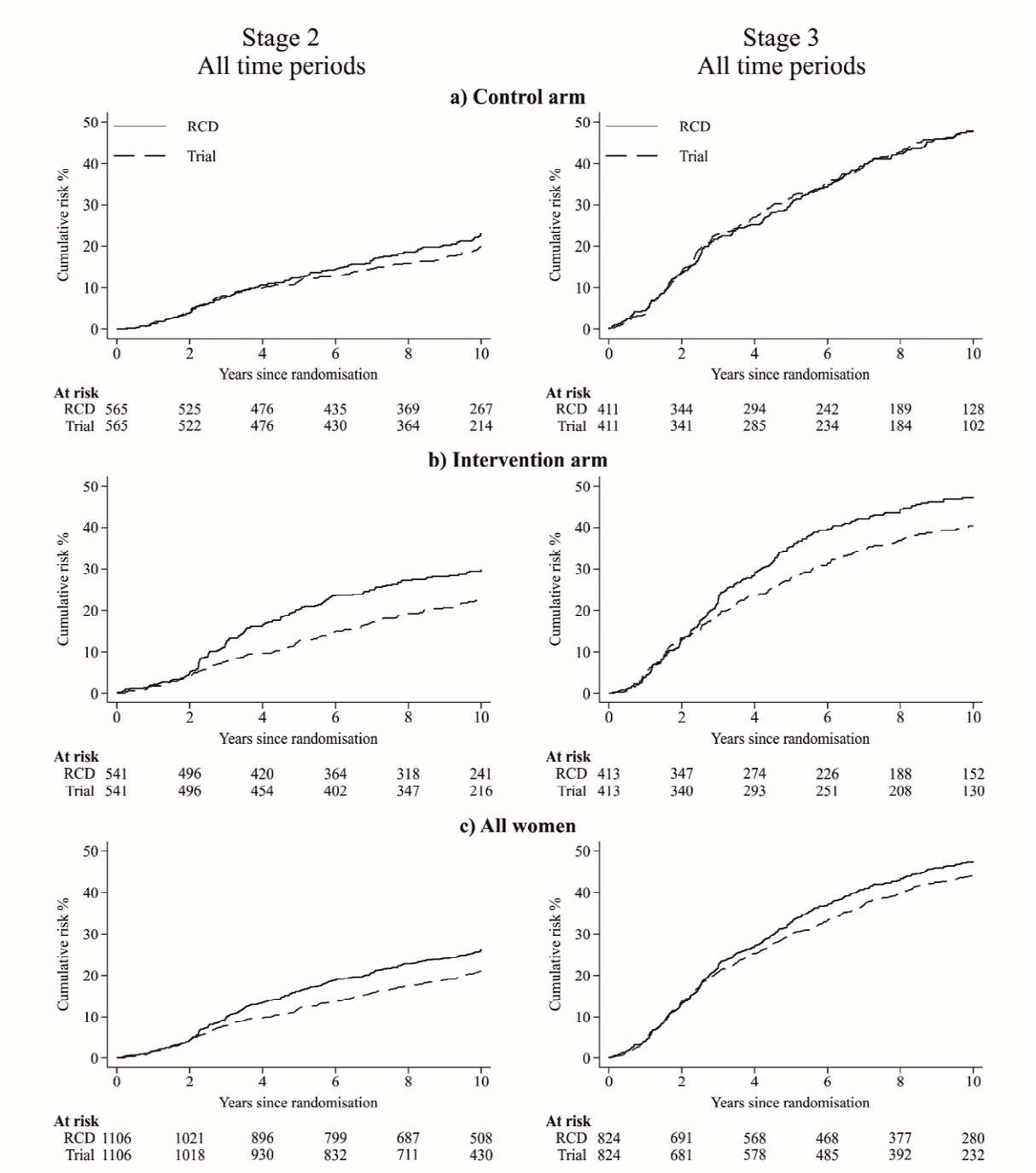


**Figure S8. Internal Validation exercise: Cumulative risk of distant recurrence in AZURE trial (dashed lines) and in the routinely collected data (RCD) (solid lines), split by stage of disease. Analyses are by randomisation arm (a and b), and for all women included in the internal validation group (c).**

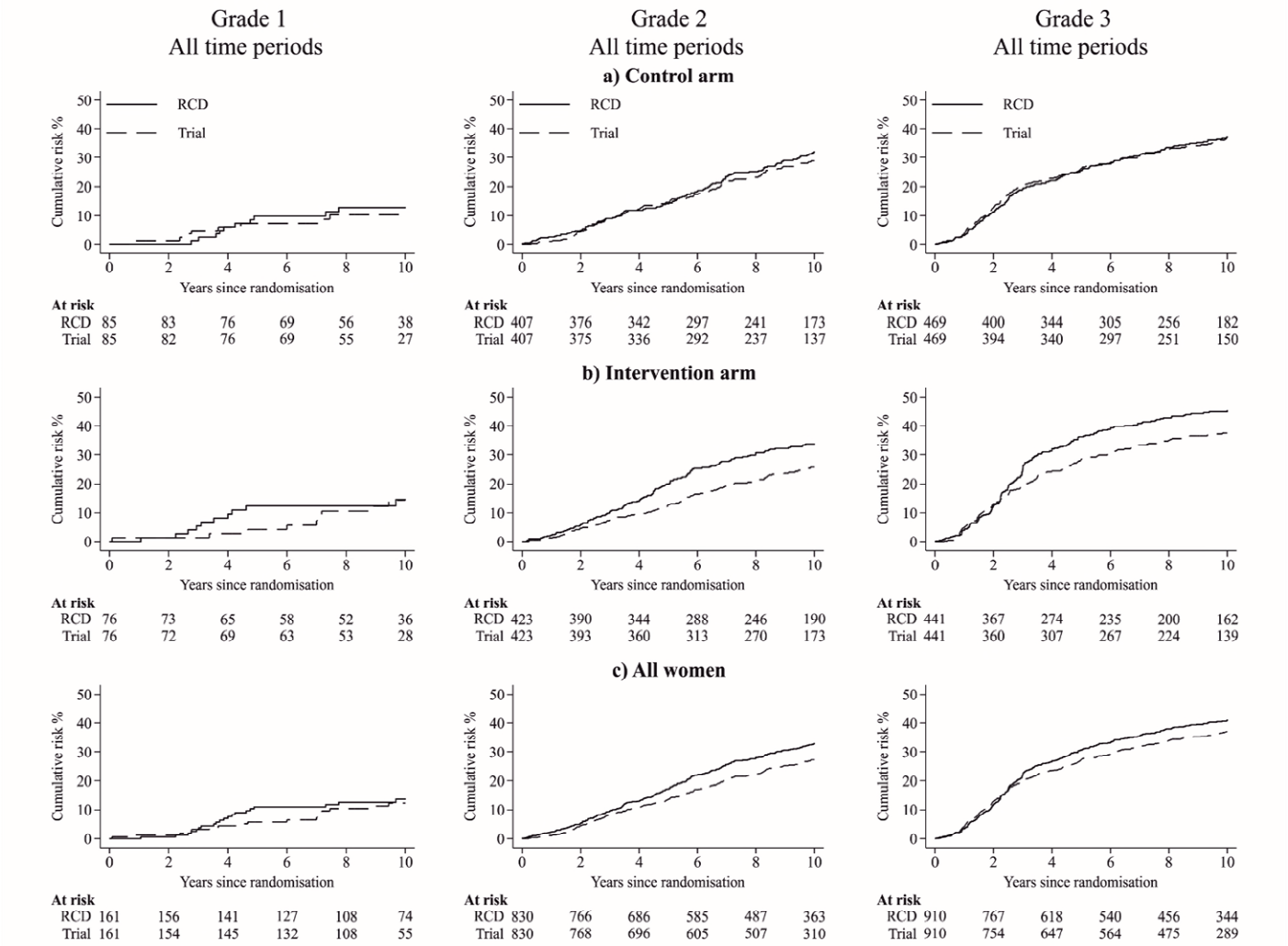


**Figure S9. Internal Validation exercise: Cumulative risk of distant recurrence in AZURE trial (dashed lines) and in the routinely collected data (RCD) (solid lines), split by tumour grade. Analyses are by randomisation arm (a and b), and for all women included in the internal validation group (c). 29 women with unknown grade excluded from plots.**

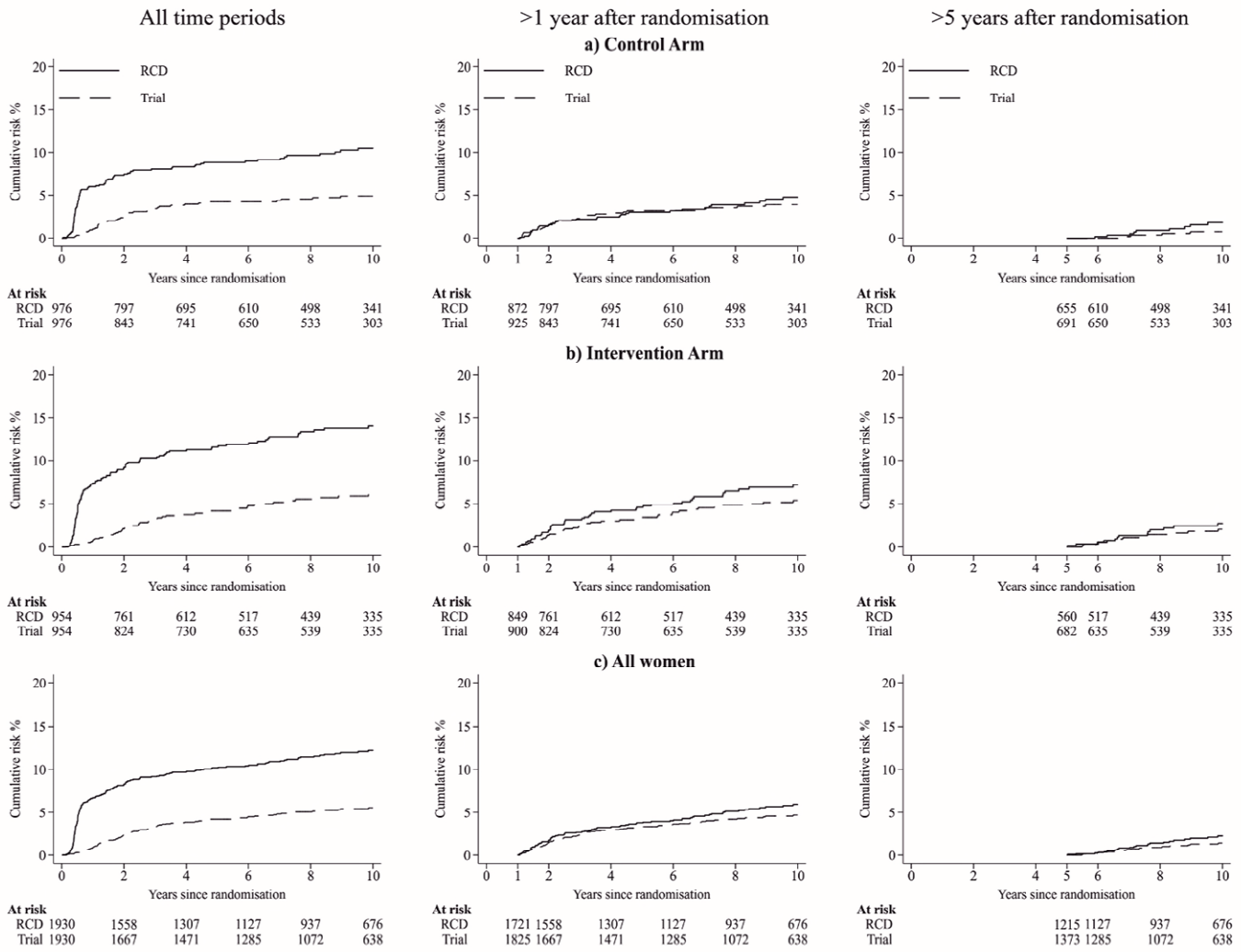


**Figure S10. Internal validation exercise: Cumulative risk of locoregional recurrence in AZURE trial (dashed lines) and in routinely collected data (RCD) (solid lines). Analyses are by separate randomisation arm (a and b), and for all 1930 women included in the internal validation group (c**). The outcome of locoregional recurrence is defined in Table S4. Plotted values at 1-, 3-, 5- and 10-years (and 95% confidence intervals) are in Table S18.

**Table S18. Internal validation exercise: Number of events and cumulative risks of locoregional recurrence by time since randomisation and AZURE trial arm, for routinely collected data (RCD) and AZURE trial data.** Calculated for all 1930 women in the internal validation group.

| | | | All time periods | | | >1 year after randomisation | | | >5 years after randomisation | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Trial Arm** | **Dataset** | **Time since randomisation (years)** | **No. women at risk[a]** | **No. events[b]** | **Cumulative risk[c] % (95% CI)** | **No. women at risk[a]** | **No. events[b]** | **Cumulative risk[c] % (95% CI)** | **No. women at risk[a]** | **No. events[b]** | **Cumulative risk[c] % (95% CI)** |
| **Control** | RCD | 0-1 | 976 | 57 | 6.0 (4.6, 7.7) | - | - | - | - | - | - |
| | | 1-3 | 872 | 18 | 8.1 (6.5, 10.0) | 872 | 18 | 2.2 (1.4, 3.5) | - | - | - |
| | | 3-5 | 736 | 6 | 8.9 (7.2, 10.9) | 736 | 6 | 3.1 (2.1, 4.5) | - | - | - |
| | | 5-10 | 655 | 9 | 10.5 (8.6, 12.8) | 655 | 9 | 4.8 (3.4, 6.7) | 655 | 9 | 1.8 (0.9, 3.4) |
| | Trial | 0-1 | 976 | 10 | 1.0 (0.6, 1.9) | - | - | - | - | - | - |
| | | 1-3 | 925 | 21 | 3.5 (2.4, 4.9) | 925 | 21 | 2.4 (1.6, 3.7) | - | - | - |
| | | 3-5 | 782 | 6 | 4.2 (3.1, 5.8) | 782 | 6 | 3.2 (2.2, 4.7) | - | - | - |
| | | 5-10 | 691 | 4 | 5.0 (3.7, 6.8) | 691 | 4 | 4.0 (2.8, 5.7) | 691 | 4 | 0.8 (0.3, 2.1) |
| **Intervention** | RCD | 0-1 | 954 | 69 | 7.4 (5.9, 9.2) | - | - | - | - | - | - |
| | | 1-3 | 849 | 25 | 10.4 (8.5, 12.5) | 849 | 25 | 3.2 (2.2, 4.7) | - | - | - |
| | | 3-5 | 673 | 9 | 11.7 (9.7, 14.0) | 673 | 9 | 4.6 (3.3, 6.4) | - | - | - |
| | | 5-10 | 560 | 13 | 14.2 (11.9, 16.9) | 560 | 13 | 7.4 (5.5, 9.8) | 560 | 13 | 2.9 (1.7, 4.9) |
| | Trial | 0-1 | 954 | 7 | 0.8 (0.4, 1.6) | - | - | - | - | - | - |
| | | 1-3 | 900 | 20 | 3.1 (2.1, 4.5) | 900 | 20 | 2.4 (1.5, 3.6) | - | - | - |
| | | 3-5 | 772 | 8 | 4.2 (3.0, 5.8) | 772 | 8 | 3.4 (2.4, 4.9) | - | - | - |
| | | 5-10 | 682 | 12 | 6.4 (4.8, 8.5) | 682 | 12 | 5.7 (4.2, 7.7) | 682 | 12 | 2.3 (1.3, 4.1) |
| **Total** | RCD | 0-1 | 1930 | 126 | 6.7 (5.6, 7.9) | - | - | - | - | - | - |
| | | 1-3 | 1721 | 43 | 9.2 (8.0, 10.6) | 1721 | 43 | 2.7 (2.0, 3.6) | - | - | - |
| | | 3-5 | 1409 | 15 | 10.2 (8.9, 11.7) | 1409 | 15 | 3.8 (3.0, 4.9) | - | - | - |
| | | 5-10 | 1215 | 22 | 12.3 (10.8, 14.0) | 1215 | 22 | 6.0 (4.8, 7.5) | 1215 | 22 | 2.3 (1.5, 3.5) |
| | Trial | 0-1 | 1930 | 17 | 0.9 (0.6, 1.4) | - | - | - | - | - | - |
| | | 1-3 | 1825 | 41 | 3.3 (2.5, 4.2) | 1825 | 41 | 2.4 (1.8, 3.2) | - | - | - |
| | | 3-5 | 1554 | 14 | 4.2 (3.3, 5.3) | 1554 | 14 | 3.3 (2.6, 4.3) | - | - | - |
| | | 5-10 | 1373 | 16 | 5.7 (4.6, 7.0) | 1373 | 16 | 4.9 (3.8, 6.1) | 1373 | 16 | 1.6 (1.0, 2.6) |

[a] Number of women at risk at start of time category
[b] Number of events during time category
[c] Cumulative risk at end of time category

**Table S19. Internal validation exercise: Agreement of routinely collected data (RCD) and AZURE trial data for locoregional recurrence.**
Calculations performed for all 1930 women in the internal validation group.

| Locoregional recurrence[a] | Analysis period and trial arm | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | All time periods | | | >1 year after randomisation[b] | | | >5 years after randomisation[b] | | |
| | Control (N=976) | Intervention (N=954) | Total (N=1930) | Control (N=976) | Intervention (N=954) | Total (N=1930) | Control (N=976) | Intervention (N=954) | Total (N=1930) |
| | | | | | No. | | | | |
| Event in both datasets | 20 | 20 | 40 | 16 | 16 | 32 | 3 | 4 | 7 |
| Event only in trial data | 21 | 27 | 48 | 14 | 22 | 36 | 1 | 4 | 5 |
| Event only in RCD | 70 | 96 | 166 | 16 | 30 | 46 | 6 | 9 | 15 |
| No event in either dataset | 865 | 811 | 1676 | 812 | 762 | 1574 | 618 | 527 | 1145 |
| **Censored before analysis period** | | | | | | | | | |
| Only in trial data | 0 | 0 | 0 | 14 | 19 | 33 | 27 | 16 | 43 |
| Only in RCD | 0 | 0 | 0 | 67 | 70 | 137 | 63 | 138 | 201 |
| In both datasets | 0 | 0 | 0 | 37 | 35 | 72 | 258 | 256 | 514 |
| **Time difference when event present in both datasets** | | | | | **No. (%)** | | | | |
| <6 months | 17 (85.0%) | 19 (95.0%) | 36 (90.0%) | 14 (87.5%) | 16 (100%) | 30 (93.8%) | 3 (100%) | 4 (100%) | 7 (100%) |
| 6-12 months | 2 (10.0%) | 0 (0.0%) | 2 (5.0%) | 2 (12.5%) | 0 (0.0%) | 2 (6.2%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| >1 year | 1 (5.0%) | 1 (5.0%) | 2 (5.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| **Performance measures[c]** | | | | | **% (95% CI)** | | | | |
| *All time periods* | | | | | | | | | |
| Sensitivity | 48.8 (33.5, 64.1) | 42.6 (28.4, 56.7) | 45.5 (35.1, 55.9) | 53.3 (35.5, 71.2) | 42.1 (26.4, 57.8) | 47.1 (35.2, 58.9) | 75.0 (32.6, 100) | 50.0 (15.4, 84.6) | 58.3 (30.4, 86.2) |
| Specificity | 92.5 (90.8, 94.2) | 89.4 (87.4, 91.4) | 91.0 (89.7, 92.3) | 98.1 (97.1, 99.0) | 96.2 (94.9, 97.5) | 97.2 (96.4, 98.0) | 99.0 (98.3, 99.8) | 98.3 (97.2, 99.4) | 98.7 (98.1, 99.4) |
| PPV | 22.2 (13.6, 30.8) | 17.2 (10.4, 24.1) | 19.4 (14.0, 24.8) | 50.0 (32.7, 67.3) | 34.8 (21.0, 48.5) | 41.0 (30.1, 51.9) | 33.3 (2.5, 64.1) | 30.8 (5.7, 55.9) | 31.8 (12.4, 51.3) |
| NPV | 97.6 (96.6, 98.6) | 96.8 (95.6, 98.0) | 97.2 (96.4, 98.0) | 98.3 (97.4, 99.2) | 97.2 (96.0, 98.3) | 97.8 (97.0, 98.5) | 99.8 (99.5, 100) | 99.2 (98.5, 100) | 99.6 (99.2, 99.9) |
| *Within 6 months of trial data* | | | | | | | | | |
| Sensitivity | 41.5 (26.4, 56.5) | 40.4 (26.4, 54.5) | 40.9 (30.6, 51.2) | 46.7 (28.8, 64.5) | 42.1 (26.4, 57.8) | 44.1 (32.3, 55.9) | 75.0 (32.6, 100) | 50.0 (15.4, 84.6) | 58.3 (30.4, 86.2) |
| Specificity | 92.5 (90.8, 94.2) | 89.4 (87.4, 91.4) | 91.0 (89.7, 92.3) | 98.1 (97.1, 99.0) | 96.2 (94.9, 97.5) | 97.2 (96.4, 98.0) | 99.0 (98.3, 99.8) | 98.3 (97.2, 99.4) | 98.7 (98.1, 99.4) |
| PPV | 19.5 (11.2, 27.9) | 16.5 (9.7, 23.3) | 17.8 (12.5, 23.1) | 46.7 (28.8, 64.5) | 34.8 (21.0, 48.5) | 39.5 (28.5, 50.5) | 33.3 (2.5, 64.1) | 30.8 (5.7, 55.9) | 31.8 (12.4, 51.3) |
| NPV | 97.3 (96.2, 98.4) | 96.7 (95.4, 97.9) | 97.0 (96.2, 97.8) | 98.1 (97.1, 99.0) | 97.2 (96.0, 98.3) | 97.6 (96.9, 98.4) | 99.8 (99.5, 100) | 99.2 (98.5, 100) | 99.6 (99.2, 99.9) |

PPV, Positive predictive value; NPV, Negative predictive value

[a] Women are censored at contralateral breast cancer, distant metastases, non-breast cancer malignancies and death (Table S4)

[b] Analysis period starts at 1 or 5 years after randomisation

[c] Performance measures defined in footnote of Table 3

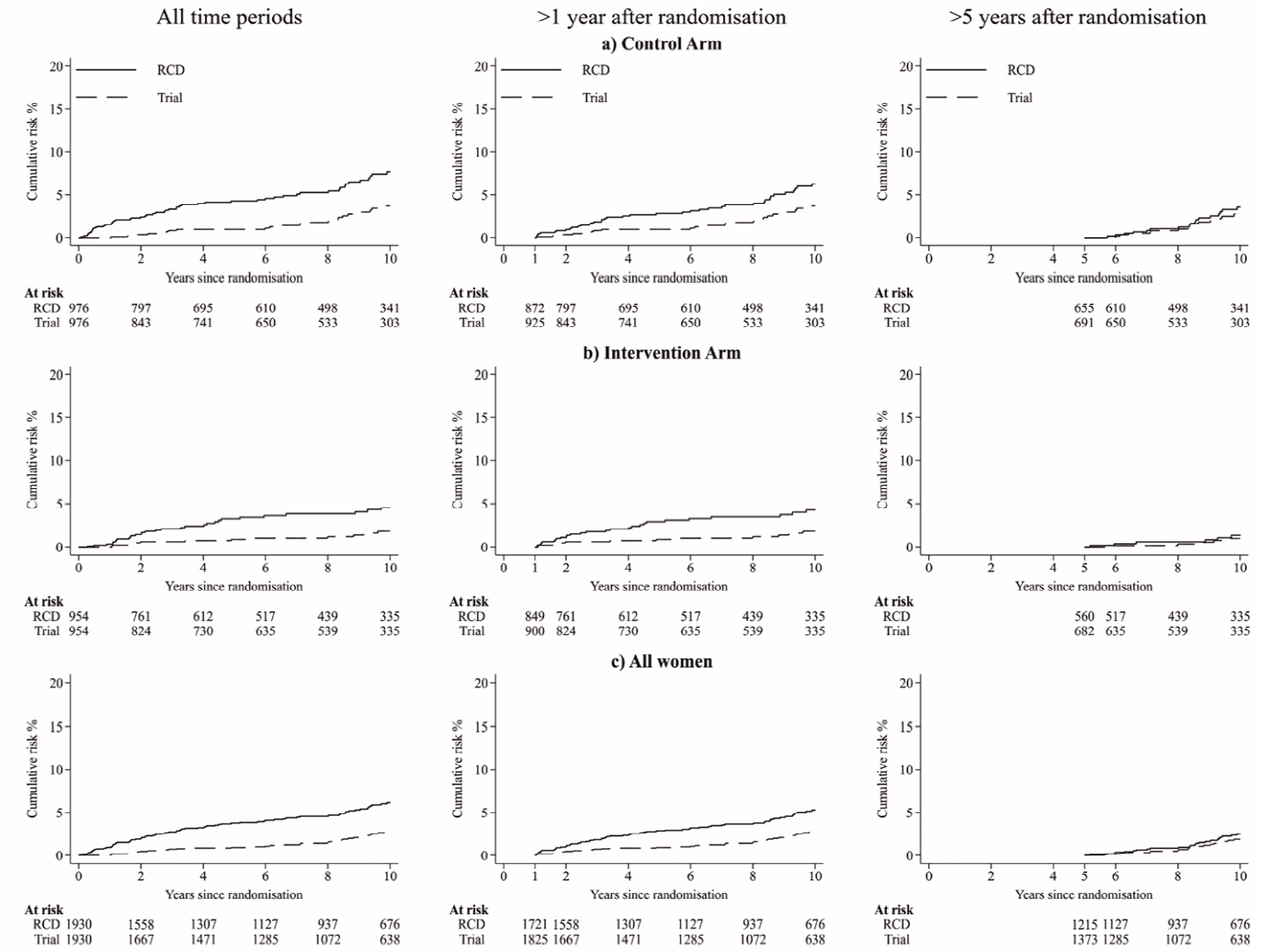


**Figure S11. Internal validation exercise: Cumulative risk of contralateral breast cancer in AZURE trial (dashed lines) and in routinely collected data (RCD) (solid lines). Analyses are by separate randomisation arm (a and b), and for all 1930 women included in the internal validation group (c).** The outcome of contralateral breast cancer is defined in Table S4. Plotted values at 1-, 3-, 5- and 10-years (and 95% confidence intervals) are in Table S20.

**Table S20. Internal validation exercise: Number of events and cumulative risks of contralateral breast cancer by time since randomisation and AZURE trial arm, for routinely collected data (RCD) and AZURE trial data.** Calculated for all 1930 women in the internal validation group.

| | | | All time periods | | | >1 year after randomisation | | | >5 years after randomisation | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Trial Arm** | **Dataset** | **Time since randomisation (years)** | **No. women at risk[a]** | **No. events[b]** | **Cumulative risk[c] % (95% CI)** | **No. women at risk[a]** | **No. events[b]** | **Cumulative risk[c] % (95% CI)** | **No. women at risk[a]** | **No. events[b]** | **Cumulative risk[c] % (95% CI)** |
| **Control** | RCD | 0-1 | 976 | 14 | 1.5 (0.9, 2.5) | - | - | - | - | - | - |
| | | 1-3 | 872 | 15 | 3.3 (2.3, 4.8) | 872 | 15 | 1.8 (1.1, 3.0) | - | - | - |
| | | 3-5 | 736 | 7 | 4.3 (3.1, 5.9) | 736 | 7 | 2.8 (1.9, 4.3) | - | - | - |
| | | 5-10 | 655 | 17 | 7.5 (5.7, 9.8) | 655 | 17 | 6.1 (4.5, 8.3) | 655 | 17 | 3.4 (2.1, 5.3) |
| | Trial | 0-1 | 976 | 0 | 0.0 (NA[d]) | - | - | - | - | - | - |
| | | 1-3 | 925 | 7 | 0.8 (0.4, 1.7) | 925 | 7 | 0.8 (0.4, 1.7) | - | - | - |
| | | 3-5 | 782 | 1 | 1.0 (0.5, 1.9) | 782 | 1 | 1.0 (0.5, 1.9) | - | - | - |
| | | 5-10 | 691 | 14 | 3.7 (2.4, 5.6) | 691 | 14 | 3.7 (2.4, 5.6) | 691 | 14 | 2.8 (1.7, 4.6) |
| **Intervention** | RCD | 0-1 | 954 | 3 | 0.3 (0.1, 1.0) | - | - | - | - | - | - |
| | | 1-3 | 849 | 14 | 2.1 (1.3, 3.4) | 849 | 14 | 1.8 (1.1, 3.1) | - | - | - |
| | | 3-5 | 673 | 7 | 3.3 (2.2, 4.8) | 673 | 7 | 2.9 (1.9, 4.5) | - | - | - |
| | | 5-10 | 560 | 6 | 4.5 (3.2, 6.5) | 560 | 6 | 4.2 (2.9, 6.2) | 560 | 6 | 1.3 (0.6, 2.9) |
| | Trial | 0-1 | 954 | 0 | 0.0 (NA[d]) | - | - | - | - | - | - |
| | | 1-3 | 900 | 5 | 0.6 (0.2, 1.4) | 900 | 5 | 0.6 (0.2, 1.4) | - | - | - |
| | | 3-5 | 772 | 2 | 0.9 (0.4, 1.8) | 772 | 2 | 0.9 (0.4, 1.8) | - | - | - |
| | | 5-10 | 682 | 5 | 1.8 (1.0, 3.3) | 682 | 5 | 1.8 (1.0, 3.3) | 682 | 5 | 1.0 (0.4, 2.3) |
| **Total** | RCD | 0-1 | 1930 | 17 | 0.9 (0.6, 1.5) | - | - | - | - | - | - |
| | | 1-3 | 1721 | 29 | 2.7 (2.1, 3.7) | 1721 | 29 | 1.8 (1.3, 2.6) | - | - | - |
| | | 3-5 | 1409 | 14 | 3.8 (2.9, 4.8) | 1409 | 14 | 2.9 (2.1, 3.9) | - | - | - |
| | | 5-10 | 1215 | 23 | 6.1 (4.9, 7.5) | 1215 | 23 | 5.2 (4.1, 6.6) | 1215 | 23 | 2.4 (1.6, 3.6) |
| | Trial | 0-1 | 1930 | 0 | 0.0 (NA[d]) | - | - | - | - | - | - |
| | | 1-3 | 1825 | 12 | 0.7 (0.4, 1.2) | 1825 | 12 | 0.7 (0.4, 1.2) | - | - | - |
| | | 3-5 | 1554 | 3 | 0.9 (0.5, 1.5) | 1554 | 3 | 0.9 (0.5, 1.5) | - | - | - |
| | | 5-10 | 1373 | 19 | 2.8 (2.0, 3.9) | 1373 | 19 | 2.8 (2.0, 3.9) | 1373 | 19 | 1.9 (1.2, 2.9) |

[a] Number of women at risk at start of time category [b] Number of events during time category [c] Cumulative risk at end of time category
[d] Unable to calculate confidence interval when no events are observed

**Table S21. Internal validation exercise: Agreement of routinely collected data (RCD) and AZURE trial data for contralateral breast cancer.**
Calculations performed for all 1930 women in the internal validation group.

| Contralateral breast cancer[a] | Analysis period and trial arm | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | All time periods | | | >1 year after randomisation[b] | | | >5 years after randomisation[b] | | |
| | Control (N=976) | Intervention (N=954) | Total (N=1930) | Control (N=976) | Intervention (N=954) | Total (N=1930) | Control (N=976) | Intervention (N=954) | Total (N=1930) |
| | | | | | No. | | | | |
| Event in both datasets | 18 | 8 | 26 | 18 | 8 | 26 | 13 | 2 | 15 |
| Event only in trial data | 4 | 4 | 8 | 2 | 3 | 5 | 1 | 1 | 2 |
| Event only in RCD | 35 | 22 | 57 | 20 | 18 | 38 | 4 | 3 | 7 |
| No event in either dataset | 919 | 920 | 1839 | 818 | 801 | 1619 | 610 | 538 | 1148 |
| **Censored before analysis period** | | | | | | | | | |
| Only in trial data | 0 | 0 | 0 | 14 | 19 | 33 | 27 | 16 | 43 |
| Only in RCD | 0 | 0 | 0 | 67 | 70 | 137 | 63 | 138 | 201 |
| In both datasets | 0 | 0 | 0 | 37 | 35 | 72 | 258 | 256 | 514 |
| **Time difference when event present in both datasets** | | | | | **No. (%)** | | | | |
| <6 months | 18 (100%) | 8 (100%) | 26 (100%) | 18 (100%) | 8 (100%) | 26 (100%) | 13 (100%) | 2 (100%) | 15 (100%) |
| 6-12 months | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| >1 year | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| **Performance measures[c]** | | | | | **% (95% CI)** | | | | |
| *All time periods* | | | | | | | | | |
| Sensitivity | 81.8 (65.7, 97.9) | 66.7 (40.0, 93.3) | 76.5 (62.2, 90.7) | 90.0 (76.9, 100) | 72.7 (46.4, 99.0) | 83.9 (70.9, 96.8) | 92.9 (79.4, 100) | 66.7 (13.3, 100) | 88.2 (72.9, 100) |
| Specificity | 96.3 (95.1, 97.5) | 97.7 (96.7, 98.6) | 97.0 (96.2, 97.8) | 97.6 (96.6, 98.6) | 97.8 (96.8, 98.8) | 97.7 (97.0, 98.4) | 99.3 (98.7, 100) | 99.4 (98.8, 100) | 99.4 (98.9, 99.8) |
| PPV | 34.0 (21.2, 46.7) | 26.7 (10.8, 42.5) | 31.3 (21.3, 41.3) | 47.4 (31.5, 63.2) | 30.8 (13.0, 48.5) | 40.6 (28.6, 52.7) | 76.5 (56.3, 96.6) | 40.0 (0.0, 82.9) | 68.2 (48.7, 87.6) |
| NPV | 99.6 (99.1, 100) | 99.6 (99.1, 100) | 99.6 (99.3, 99.9) | 99.8 (99.4, 100) | 99.6 (99.2, 100) | 99.7 (99.4, 100) | 99.8 (99.5, 100) | 99.8 (99.5, 100) | 99.8 (99.6, 100) |
| *Within 6 months of trial data* | | | | | | | | | |
| Sensitivity | 81.8 (65.7, 97.9) | 66.7 (40.0, 93.3) | 76.5 (62.2, 90.7) | 90.0 (76.9, 100) | 72.7 (46.4, 99.0) | 83.9 (70.9, 96.8) | 92.9 (79.4, 100) | 66.7 (13.3, 100) | 88.2 (72.9, 100) |
| Specificity | 96.3 (95.1, 97.5) | 97.7 (96.7, 98.6) | 97.0 (96.2, 97.8) | 97.6 (96.6, 98.6) | 97.8 (96.8, 98.8) | 97.7 (97.0, 98.4) | 99.3 (98.7, 100) | 99.4 (98.8, 100) | 99.4 (98.9, 99.8) |
| PPV | 34.0 (21.2, 46.7) | 26.7 (10.8, 42.5) | 31.3 (21.3, 41.3) | 47.4 (31.5, 63.2) | 30.8 (13.0, 48.5) | 40.6 (28.6, 52.7) | 76.5 (56.3, 96.6) | 40.0 (0.0, 82.9) | 68.2 (48.7, 87.6) |
| NPV | 99.6 (99.1, 100) | 99.6 (99.1, 100) | 99.6 (99.3, 99.9) | 99.8 (99.4, 100) | 99.6 (99.2, 100) | 99.7 (99.4, 100) | 99.8 (99.5, 100) | 99.8 (99.5, 100) | 99.8 (99.6, 100) |

PPV, Positive predictive value; NPV, Negative predictive value

[a] Women are censored at locoregional recurrence, distant metastases, non-breast cancer malignancies and death (Table S4)

[b] Analysis period starts at 1 or 5 years after randomisation

[c] Performance measures defined in footnote of Table 3

**Table S22. Internal validation exercise: Number of events and cumulative risks of any recurrence by time since randomisation and AZURE trial arm, for routinely collected data (RCD) and AZURE trial data.** Calculated for all 1930 women in the internal validation group.

| Trial Arm and Dataset | Time since random-isation (years) | All time periods | | | >1 year after randomisation | | | >5 years after randomisation | | | All time periods with post-validation adjustment | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. women at risk[a] | No. events[b] | Cumulative risk[c] % (95% CI) | No. women at risk[a] | No. events[b] | Cumulative risk[c] % (95% CI) | No. women at risk[a] | No. events[b] | Cumulative risk[c] % (95% CI) | No. women at risk[a] | No. events[b] | Cumulative risk[c] % (95% CI) |
| **Control** | | | | | | | | | | | | | |
| RCD | 0-1 | 976 | 107 | 11.0 (9.2, 13.2) | - | - | - | - | - | - | 976 | 27 | 2.8 (1.9, 4.0) |
| | 1-3 | 857 | 128 | 24.5 (21.9, 27.3) | 857 | 128 | 15.1 (12.9, 17.7) | - | - | - | 936 | 132 | 16.7 (14.4, 19.2) |
| | 3-5 | 709 | 56 | 30.5 (27.7, 33.6) | 709 | 56 | 21.9 (19.3, 24.9) | - | - | - | 783 | 65 | 23.7 (21.1, 26.5) |
| | 5-10 | 631 | 100 | 43.6 (40.4, 47.0) | 631 | 100 | 36.6 (33.3, 40.2) | 631 | 100 | 18.8 (15.7, 22.4) | 693 | 115 | 38.6 (35.4, 42.0) |
| Trial | 0-1 | 976 | 32 | 3.3 (2.4, 4.6) | - | - | - | - | - | - | 976 | 32 | 3.3 (2.4, 4.6) |
| | 1-3 | 925 | 124 | 16.4 (14.2, 18.9) | 925 | 124 | 13.5 (11.5, 15.9) | - | - | - | 925 | 124 | 16.4 (14.2, 18.9) |
| | 3-5 | 782 | 52 | 22.1 (19.6, 24.9) | 782 | 52 | 19.4 (17.0, 22.2) | - | - | - | 782 | 52 | 22.1 (19.6, 24.9) |
| | 5-10 | 691 | 94 | 35.6 (32.4, 39.0) | 691 | 94 | 33.4 (30.2, 36.8) | 691 | 94 | 17.3 (14.4, 20.7) | 691 | 94 | 35.6 (32.4, 39.0) |
| **Intervention** | | | | | | | | | | | | | |
| RCD | 0-1 | 954 | 108 | 11.4 (9.5, 13.6) | - | - | - | - | - | - | 954 | 28 | 3.0 (2.1, 4.3) |
| | 1-3 | 835 | 181 | 30.8 (28.0, 33.9) | 835 | 181 | 22.0 (19.3, 24.9) | - | - | - | 909 | 166 | 20.9 (18.4, 23.7) |
| | 3-5 | 633 | 97 | 41.6 (38.5, 44.9) | 633 | 97 | 34.1 (31.0, 37.5) | - | - | - | 719 | 117 | 34.0 (31.0, 37.2) |
| | 5-10 | 512 | 87 | 52.9 (49.6, 56.2) | 512 | 87 | 46.8 (43.3, 50.4) | 512 | 87 | 19.2 (15.9, 23.2) | 576 | 96 | 46.6 (43.3, 50.0) |
| Trial | 0-1 | 954 | 33 | 3.5 (2.5, 4.9) | - | - | - | - | - | - | 954 | 33 | 3.5 (2.5, 4.9) |
| | 1-3 | 900 | 104 | 14.8 (12.7, 17.3) | 900 | 104 | 11.7 (9.8, 14.0) | - | - | - | 900 | 104 | 14.8 (12.7, 17.3) |
| | 3-5 | 772 | 59 | 21.4 (18.9, 24.3) | 772 | 59 | 18.6 (16.2, 21.3) | - | - | - | 772 | 59 | 21.4 (18.9, 24.3) |
| | 5-10 | 682 | 88 | 34.0 (30.8, 37.4) | 682 | 88 | 31.6 (28.4, 35.0) | 682 | 88 | 15.9 (13.1, 19.3) | 682 | 88 | 34.0 (30.8, 37.4) |
| **Total** | | | | | | | | | | | | | |
| RCD | 0-1 | 1930 | 215 | 11.2 (9.9, 12.7) | - | - | - | - | - | - | 1930 | 55 | 2.9 (2.2, 3.7) |
| | 1-3 | 1692 | 309 | 27.6 (25.7, 29.7) | 1692 | 309 | 18.5 (16.7, 20.4) | - | - | - | 1845 | 298 | 18.8 (17.1, 20.6) |
| | 3-5 | 1342 | 153 | 36.0 (33.9, 38.2) | 1342 | 153 | 27.9 (25.8, 30.2) | - | - | - | 1502 | 182 | 28.8 (26.8, 30.9) |
| | 5-10 | 1143 | 187 | 48.2 (45.8, 50.6) | 1143 | 187 | 41.6 (39.2, 44.2) | 1143 | 187 | 19.0 (16.7, 21.6) | 1269 | 211 | 42.5 (40.2, 44.9) |
| Trial | 0-1 | 1930 | 65 | 3.4 (2.7, 4.3) | - | - | - | - | - | - | 1930 | 65 | 3.4 (2.7, 4.3) |
| | 1-3 | 1825 | 228 | 15.6 (14.0, 17.3) | 1825 | 228 | 12.6 (11.2, 14.3) | - | - | - | 1825 | 228 | 15.6 (14.0, 17.3) |
| | 3-5 | 1554 | 111 | 21.8 (20.0, 23.7) | 1554 | 111 | 19.0 (17.3, 20.9) | - | - | - | 1554 | 111 | 21.8 (20.0, 23.7) |
| | 5-10 | 1373 | 182 | 34.8 (32.5, 37.1) | 1373 | 182 | 32.5 (30.2, 34.9) | 1373 | 182 | 16.6 (14.5, 18.9) | 1373 | 182 | 34.8 (32.5, 37.1) |

[a] Number of women at risk at start of time category [b] Number of events during time category [c] Cumulative risk at end of time category

**Table S23. Internal validation exercise: Number of events and cumulative risks of breast cancer mortality and all-cause mortality by time since randomisation and AZURE trial arm, for routinely collected data (RCD) and AZURE trial data.** Calculated for all 1930 women in the internal validation group.

| Trial Arm | Dataset | Time since randomisation (years) | Breast cancer mortality | | | All-cause mortality | | |
|---|---|---|---|---|---|---|---|---|
| | | | No. women at risk[a] | No. events[b] | Cumulative risk[c] % (95% CI) | No. women at risk[a] | No. events[b] | Cumulative risk[c] % (95% CI) |
| **Control** | RCD | 0-1 | 976 | 9 | 0.9 (0.5, 1.8) | 976 | 14 | 1.4 (0.9, 2.4) |
| | | 1-3 | 954 | 59 | 7.1 (5.6, 8.9) | 954 | 64 | 8.1 (6.5, 10.0) |
| | | 3-5 | 878 | 64 | 14.0 (11.9, 16.4) | 878 | 70 | 15.5 (13.4, 18.0) |
| | | 5-10 | 786 | 82 | 24.6 (21.8, 27.6) | 786 | 105 | 28.6 (25.7, 31.7) |
| | Trial | 0-1 | 976 | 8 | 0.8 (0.4, 1.6) | 976 | 14 | 1.4 (0.9, 2.4) |
| | | 1-3 | 951 | 61 | 7.2 (5.8, 9.1) | 951 | 65 | 8.2 (6.6, 10.1) |
| | | 3-5 | 876 | 61 | 13.8 (11.8, 16.2) | 876 | 68 | 15.5 (13.3, 17.9) |
| | | 5-10 | 778 | 90 | 26.5 (23.6, 29.7) | 778 | 105 | 29.8 (26.8, 33.0) |
| **Intervention** | RCD | 0-1 | 954 | 9 | 1.0 (0.5, 1.8) | 954 | 13 | 1.4 (0.8, 2.3) |
| | | 1-3 | 930 | 58 | 7.2 (5.7, 9.1) | 930 | 63 | 8.1 (6.5, 10.1) |
| | | 3-5 | 846 | 49 | 12.7 (10.7, 15.0) | 846 | 58 | 14.5 (12.4, 16.9) |
| | | 5-10 | 768 | 95 | 24.9 (22.1, 28.0) | 768 | 111 | 28.3 (25.4, 31.5) |
| | Trial | 0-1 | 954 | 7 | 0.7 (0.4, 1.5) | 954 | 12 | 1.3 (0.7, 2.2) |
| | | 1-3 | 929 | 60 | 7.2 (5.7, 9.1) | 929 | 64 | 8.1 (6.6, 10.1) |
| | | 3-5 | 844 | 51 | 12.9 (10.9, 15.3) | 844 | 58 | 14.5 (12.4, 17.0) |
| | | 5-10 | 767 | 98 | 26.6 (23.7, 29.9) | 767 | 112 | 29.7 (26.7, 33.0) |
| **Total** | RCD | 0-1 | 1930 | 18 | 0.9 (0.6, 1.5) | 1930 | 27 | 1.4 (1.0, 2.0) |
| | | 1-3 | 1884 | 117 | 7.2 (6.1, 8.4) | 1884 | 127 | 8.1 (7.0, 9.4) |
| | | 3-5 | 1724 | 113 | 13.3 (11.9, 15.0) | 1724 | 128 | 15.0 (13.5, 16.7) |
| | | 5-10 | 1554 | 177 | 24.7 (22.8, 26.9) | 1554 | 216 | 28.5 (26.4, 30.7) |
| | Trial | 0-1 | 1930 | 15 | 0.8 (0.5, 1.3) | 1930 | 26 | 1.4 (0.9, 2.0) |
| | | 1-3 | 1880 | 121 | 7.2 (6.2, 8.5) | 1880 | 129 | 8.2 (7.0, 9.5) |
| | | 3-5 | 1720 | 112 | 13.4 (11.9, 15.0) | 1720 | 126 | 15.0 (13.5, 16.7) |
| | | 5-10 | 1545 | 188 | 26.6 (24.5, 28.8) | 1545 | 217 | 29.8 (27.6, 32.0) |

[a] Number of women at risk at the start of the time category
[b] Number of events during time category
[c] Cumulative risk at end of time category

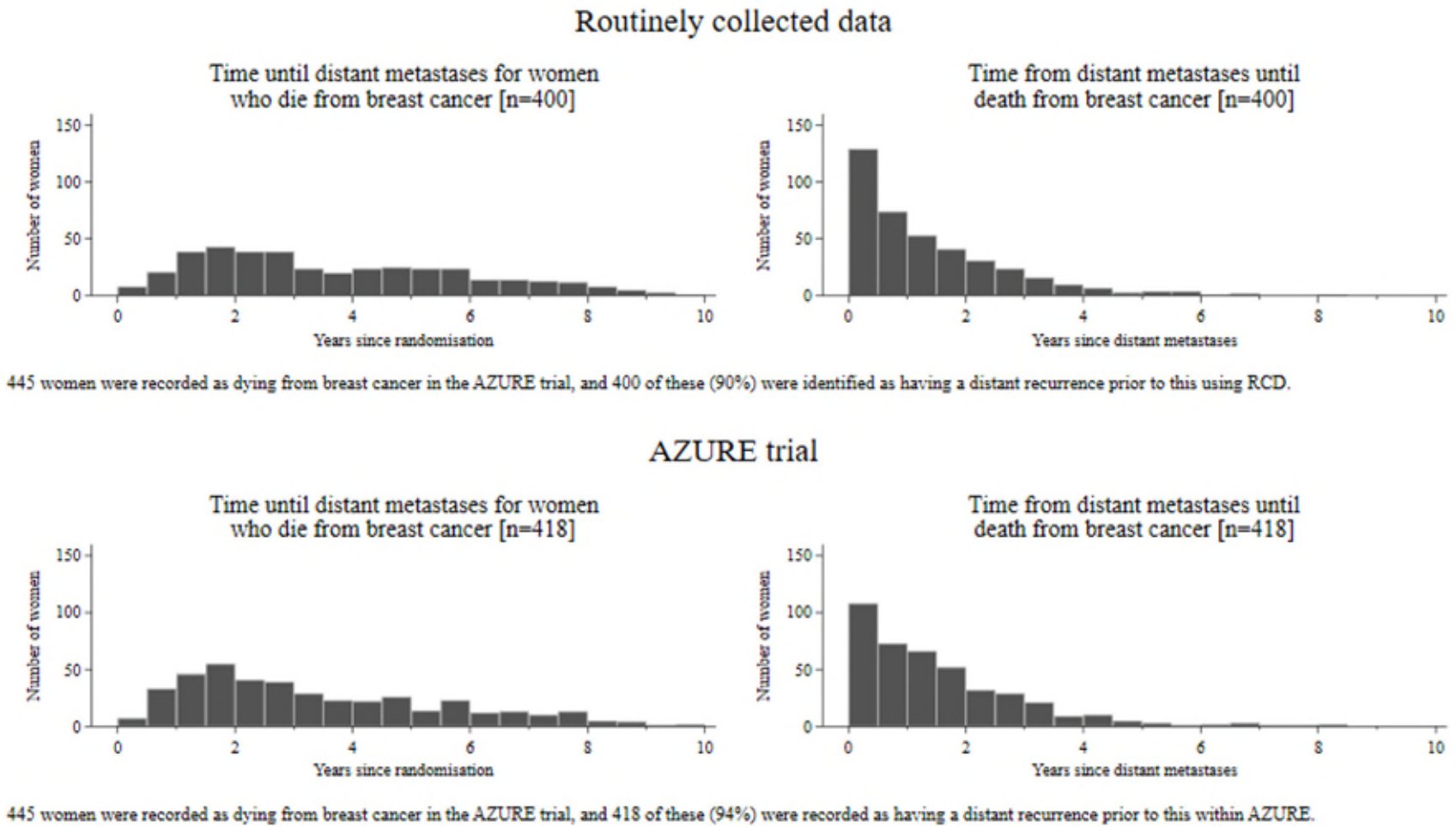


**Figure S12. Internal validation exercise: Distribution of time until distant metastasis and then to death from breast cancer for 445 women recorded as dying from breast cancer in trial data.**

**Table S24. Internal validation exercise: Agreement of routinely collected data (RCD) and AZURE trial data for breast cancer mortality and all-cause mortality, by AZURE trial arm.** Calculations performed for all 1930 women in the internal validation group.

| | Outcome and trial arm | | | | | |
|---|---|---|---|---|---|---|
| | Breast cancer mortality[a] | | | All-cause mortality | | |
| | Control (N=976) | Intervention (N=954) | Total (N=1930) | Control (N=976) | Intervention (N=954) | Total (N=1930) |
| | No. | | | | | |
| Event in both datasets | 210 | 210 | 420 | 260 | 250 | 510 |
| Event only in trial data | 17 | 8 | 25[b] | 0 | 1 | 1[c] |
| Event only in RCD | 10 | 4 | 14[d] | 1 | 1 | 2[e] |
| No event in either dataset | 739 | 732 | 1471 | 715 | 702 | 1417 |
| **Time difference when event present in both datasets** | | | **No. (%)** | | | |
| <6 months | 210 (100%) | 209 (99.5%) | 419 (99.8%) | 260 (100%) | 249 (99.6%) | 509 (99.8%) |
| 6-12 months | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| >1 year | 0 (0.0%) | 1 (0.5%) | 1 (0.2%) | 0 (0.0%) | 1 (0.4%) | 1 (0.2%) |
| **Performance measures[f]** | | | **% (95% CI)** | | | |
| *All time periods* | | | | | | |
| Sensitivity | 92.5 (89.1, 95.9) | 96.3 (93.8, 98.8) | 94.4 (92.2, 96.5) | 100 (100, 100) | 99.6 (98.8, 100) | 99.8 (99.4, 100) |
| Specificity | 98.7 (97.8, 99.5) | 99.5 (98.9, 100) | 99.1 (98.6, 99.5) | 99.9 (99.6, 100) | 99.9 (99.6, 100) | 99.9 (99.7, 100) |
| PPV | 95.5 (92.7, 98.2) | 98.1 (96.3, 99.9) | 96.8 (95.1, 98.4) | 99.6 (98.9, 100) | 99.6 (98.8, 100) | 99.6 (99.1, 100) |
| NPV | 97.8 (96.7, 98.8) | 98.9 (98.2, 99.7) | 98.3 (97.7, 99.0) | 100 (100, 100) | 99.9 (99.6, 100) | 99.9 (99.8, 100) |
| *Within 6 months of trial data* | | | | | | |
| Sensitivity | 92.5 (89.1, 95.9) | 95.9 (93.2, 98.5) | 94.2 (92.0, 96.3) | 100 (100, 100) | 99.2 (98.1, 100) | 99.6 (99.1, 100) |
| Specificity | 98.7 (97.8, 99.5) | 99.5 (98.9, 100) | 99.1 (98.6, 99.5) | 99.9 (99.6, 100) | 99.9 (99.6, 100) | 99.9 (99.7, 100) |
| PPV | 95.5 (92.7, 98.2) | 98.1 (96.3, 99.9) | 96.8 (95.1, 98.4) | 99.6 (98.9, 100) | 99.6 (98.8, 100) | 99.6 (99.1, 100) |
| NPV | 97.8 (96.7, 98.8) | 98.8 (98.0, 99.6) | 98.3 (97.6, 98.9) | 100 (100, 100) | 99.7 (99.3, 100) | 99.9 (99.7, 100) |

PPV, Positive predictive value; NPV, Negative predictive value

[a] Women are censored at non-breast-cancer deaths (Table S4)

[b] All had a non-breast-cancer death identified in RCD within 3 weeks of trial death: 14 were classified as death from non-breast cancer; 7 as death from cause other than cancer; and 4 of unknown cause.

[c] Trial data recorded death from cause other than cancer and the same event was identified in RCD >3 months after trial (so censored before death).

[d] 13 had a non-breast-cancer death recorded in trial data within 3 weeks of RCD breast death: 1 was a death from non-breast cancer; 6 as death from cause other than cancer; and 6 of unknown cause. 1 had no death recorded in trial data (see footnote ZZ).

[e] 1 had breast death identified in RCD after date of withdrawal from trial, and the other had death from non-breast cancer >10 years after randomisation (study endpoint). Both deaths were within the 3 month window for RCD.

[f] Performance measures defined in footnote of Table 3

**Table S25. Previous work in England comparing outcomes in routine data held by the former National Cancer Data Repository with those reported in the TACT (Taxotere and Adjuvant ChemoTherapy) trial.** Based on Kilburn et al.[1]

| | Local recurrence (N = 140) | Distant recurrence (N=691) | New breast disease[a] (N = 67) | Any breast disease[b] (N=898) |
|---|---|---|---|---|
| Agreement | 98 | 425 | 54 | 577 |
| Event reported in TACT but not in NCDR | 17 | 76 | 2 | 95 |
| Disagreement in number of sites and/or diagnosis time | 23 | 168 | 10 | 201 |
| Event occurred after 31 March 2010 (HES extract date) | 2 | 22 | 1 | 25 |
| Sensitivity excluding events where there was disagreement in number of sites and/or diagnosis time[c] | 71.0% | 63.5% | 81.8% | 66.1% |
| Sensitivity including events where there was disagreement in number of sites and/or diagnosis time[c] | 87.9% | 88.6% | 97.0% | 89.1% |

*TACT* Taxotere and Adjuvant ChemoTherapy, *NCDR* National Cancer Data Repository, *HES* Hospital Episode Statistics

[a] i.e. New breast second primary cancer, including contralateral breast cancer

[b] i.e. Local recurrence, distant recurrence, or new breast disease.

[c] Denominators exclude events occurring after 31 March 2010 (HES extract date).

Reference

1. Kilburn LS, Aresu M, Banerji J, Barrett-Lee P, Ellis P, Bliss JM. Can routine data be used to support cancer clinical trials? A historical baseline on which to build: retrospective linkage of data from the TACT (CRUK 01/001) breast cancer trial and the National Cancer Data Repository. *Trials* 2017; **18**(1): 561.