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Bias in survival estimates created by a requirement for consent to enter a clinical breast cancer registry

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ABSTRACT

Background: A requirement for consent for inclusion may bias the results from a clinical registry. This study gives a direct measure of this bias, based on a population-based clinical breast cancer registry where the requirement for consent was removed after further ethical review and data could be re-analysed.

Methods: In Auckland, New Zealand, the population-based clinical breast cancer registry required written patient consent for inclusion from 2000-2012. A subsequent ethical review removed this requirement and allowed an analysis of consented and non-consented patients. Kaplan-Meier survival to 10 years (mean follow-up 5.1 years, maximum 13.9 years), demographic and clinical characteristics were compared. Of 9244 women with invasive cancer, 926 (10.4%) were not consented, and of 1642 women with ductal carcinoma in situ, 245 (14.9%) were not consented.

Results: Survival was much higher for consenting patients; invasive cancer, 5 year survival 83.2% (95% confidence limits 82.2–84.1%) for consenting patients, 57.1% (53.0–60.9%) for non-consenting, and 80.8% in all patients. Analyses based only on consenting patients overestimate survival in all patients by around 2% at 2, 5, and 10 years. Non-consented patients were older, more often of Pacific ethnicity, had fewer screen-detected cancers, and more often had metastatic disease; they less frequently had primary surgery or systemic treatments.

Conclusion: Data from a registry requiring active consent gives an upward bias in survival results, as non-consenting patients have more extensive disease, less treatment, and lower survival. To give unbiased results active consent should be not required in a clinical cancer registry.

1. Introduction

The Auckland Breast Cancer Registry was established in June 2000 by a voluntary group led by clinicians to collect demographic, clinical and pathological data on all newly diagnosed patients with breast cancer in the Auckland region (population around 1.4 million in 2016), and to document follow-up and outcomes [1,2]. The registry is population-based, including all newly diagnosed patients with primary breast cancer resident in the defined region, and is regularly linked to the statutory national cancer registry, and to national mortality data to ascertain deaths [1,2]. From 2000–2012, individual written consent was required for patients to be included in the registry. Clinicians were requested to present the project to potential participants when seen in a clinic, and patients were asked to sign the consent form with a supporting signature by a witness. The consent form assured patients that their demographic information and data on their cancer data, treatment and follow-up would be collected using a key-coded technique suitable for potentially identifiable data, and only anonymized/unidentifiable data would be used for research and audit activities and for presentation or publication. The consent form provided assurances that there was a strict protocol to ensure confidentiality, and that participation was voluntary and would not affect the patient's care. Patients were usually approached for consent at their first visit to the specialist clinic. For some patients the process was delayed but the consent process was completed by first therapy, within 90 days of diagnosis.

By 2010, the registry management group was aware that consent was not being obtained from approximately 10% of patients. To achieve greater completeness, the group requested a review by the national statutory Health and Disability Ethics Committee, operated by the Ministry of Health, on whether the requirement for consent was

Abbreviations: C, consented; NC, non-consented; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; NHI, National Health Index number

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Table 1
Disease specific survival up to 10 years in consented and non-consented patients, for invasive cancer and for DCI.

Group and numbers	2 year			5 year			10 year		
	Number followed	Survival %	95% CI	Number followed	Survival %	95% CI	Number followed	Survival %	95% CI
Invasive cancer									
Invasive, consented, n = 8282	6906	94.2	93.6–94.7	4007	83.2	82.2–84.1	1025	69.5	68.0–71.0
Invasive, not consented, n = 962	520	78.0	75.0–80.7	228	57.1	53.0–60.9	29	40.9	35.0–46.7
All patients, n = 9244	7426	92.6	92.0–93.1	4235	80.8	79.9–81.7	1054	67.1	65.6–68.5
Difference consented to not consented		16.2	p < 0.0001		26.1	p < 0.0001		28.6	p < 0.0001
Difference consented to total		1.6			2.4			2.4	
Ductal carcinoma in situ (DCIS)									
DCIS, consented, n = 1397	1221	99.3	98.8–99.7	767	96.7	95.5–97.7	214	92.6	90.2–94.6
DCIS, not consented, n = 245	180	97.0	94.2–98.9	90	92.3	87.4–96.1	11	86.8	79.3–92.8
All patients, n = 1642	1401	99.0	98.4–99.4	857	96.1	94.9–97.2	225	91.8	89.5–93.8
Difference consented to not consented		2.3	p = 0.001		4.4	p = 0.001		5.8	p = 0.002
Difference consented to total		0.3			0.6			0.8	

required. As a result of the review, the ethics committee in July 2011 allowed the registry a dispensation to research and analyse 'non-consented data' (NC) and to compare it with 'consented data' (C). This temporary access aimed at checking whether the NC data was compromising or skewing the conclusions in the overall data. A short report comparing the consented and non-consented groups was prepared. (We will refer to patients as 'consented' rather than 'consenting', as consent requires the patient to be invited as well to give their consent.) Further ethical review following this report resulted in changes in the consent process: approval to use an opt-out approach in November 2012, and the grant of a waiver of consent in March 2013 allowing the previously non-consented data to be analysed and kept in the registry.

For this study, information on all patients diagnosed from 2000 to 2012 was accessed, including data from patients not giving active consent ('NC data'). The NC data came from those patients had not returned their consent form for any reason.

2. Methods

2.1. Patient selection and data collection

The registry data are from both patients who give consent (C) and those who did not give consent (NC) within the period 2000-2012. Eligible patients are defined by registry criteria applied at that time:

- no breast cancer history before 1st of June 2000;
- diagnosed with invasive carcinoma or ductal carcinoma in situ (DCIS) but not lobular carcinoma in situ (LCIS) alone;
- Auckland region resident at first surgery, or Auckland region resident who had first surgery outside Auckland and came back to Auckland for adjuvant treatment;
- New Zealand permanent resident (including Cook Island resident) at the time of diagnosis.

The registry collates information on baseline, treatment and follow-up data, including data on diagnosis and treatment of local/regional recurrence and metastatic disease, from both the public and private health care facilities to which registry data managers have been given access. These systems include all public hospitals, private hospitals and all private practitioners known to be treating breast cancer patients within the Auckland region. Mortality data is obtained by regular linkage by the Ministry of Health between the study database and national mortality records using the patient's unique National Health Index (NHI) number for linkage. Follow-up was until death or 31 st Dec 2012.

2.2. Statistical analysis

Consented and NC groups were compared using Kaplan Meier survival analysis, chi square and log-rank tests [3]. Direct standardisation used the whole patient group as the standard population, with confidence limits [4]. Stata statistical software (version 13) was used for the statistical analysis [5]. A sensitivity analysis, of survival left-censored at 90 days after diagnosis, thus excluding patients with less than 90 days follow-up, was done to assess the effects of bias arising from completion of the consent process being delayed up to 90 days post-diagnosis.

3. Results

3.1. Invasive cancer: survival by consent status

There were 9244 women with a first primary invasive breast cancer diagnosed between 1st June 2000 and 31st December 2012. Follow-up was mean 5.1 years, median 4.5 years, and maximum 13.9 years. Of these, 89.6% (n = 8282) women had given their active consent for inclusion in the registry (consented) and 10.4% (n = 962) had not (non-consented).

The survival of non-consented patients was substantially worse than that of patients giving consent (Table 1, Fig. 1), throughout the follow-up period. For consented patients, survival at 2, 5, and 10 years was 94.2, 83.2, and 69.5% respectively; while for non-consented patients it was 78.0, 57.1, and 40.9%, the differences at each time being significant. Overall, the log rank chi square was 370.20; P < 0.0001.

3.2. Overall survival comparing the overall cohort and consented group (invasive)

The overall survival rates for all patients are consistently lower than those of the subgroup who give active consent (Table 1), the differences at 2, 5 and 10 years respectively being 1.6, 2.4, and 2.4%. The survival rates based on all patients lie below the 95% confidence limits for the rates based only on the consented patients.

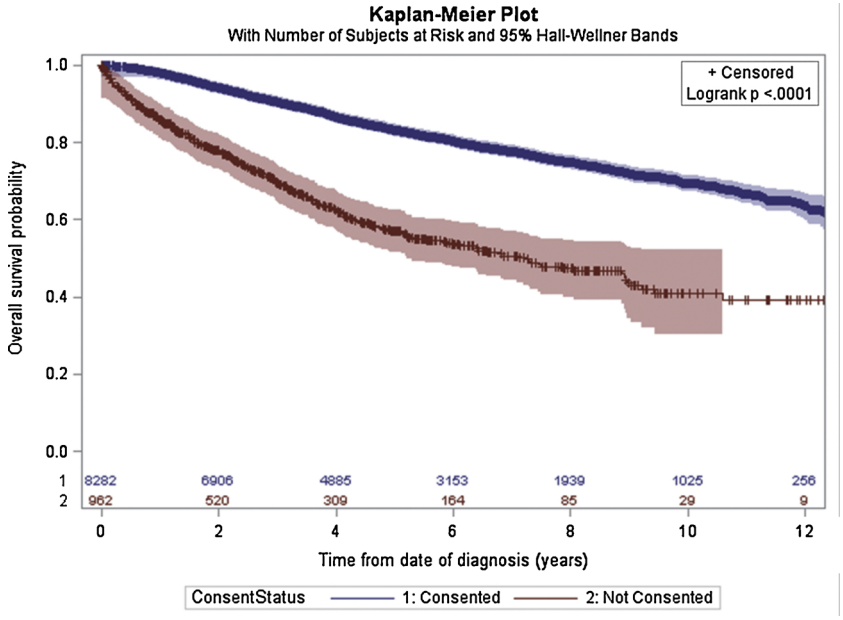

Fig. 1. Invasive cancer: disease-specific survival of consented and non-consented patients, with 95% confidence bands. Logrank statistic chisq 400.1, $p < 0.0001$.

Table 2
Proportions of patients not consented, by age and ethnicity.

		Consented	Non-consented	% non consented	95% CL		
Total		8282	962	10.4	9.8	–	11.0
Age	< = 49	2507	231	8.4	7.3	–	9.5
	50-69	4192	423	9.3	8.4	–	10.3
	70-79	993	109	10.6	8.5	–	12.7
	80+	590	199	26.5	21.6	–	31.4
Ethnicity	NZ European	5498	633	9.9	9.2	–	10.7
	Maori	629	47	9.8	6.2	–	13.4
	Pacific	616	90	14.4	11.1	–	17.6
	Asian	708	97	12.9	9.9	–	15.9
	Other	331	39	11.0	7.4	–	14.7

Age and ethnicity mutually standardised by direct method.
Subjects with missing data on ethnicity excluded (6.0% of consented, 5.8% of non-consented).

3.3. Features of consented and non-consented patients

The group of non-consented patients with invasive cancer differs from the consented group in demographic features, disease characteristics, treatment, and survival. For demographic factors, age and ethnicity are correlated. The proportions not consented increased regularly with age; after adjustment for ethnicity, from 8.4% at ages < = 49 to 26.5% at ages 80 and over, the differences being significant (Table 2). By ethnicity, adjusted for age, and compared to NZ European women (9.9% non-consented), the non-consented proportions was similar in Maori (9.8%), but significantly higher in Pacific women (14.4%). Asian women and those of 'other' ethnicities had non-significantly higher proportions than NZ Europeans.

Omitting missing data, non-consented patients had features associated with a poorer prognosis (Table 3); they were more often clinically rather than screen detected, and 13% had metastatic disease compared with 3% of consented patients. Non-consented patients more often had no primary surgery (26.2% compared with 4.0% of consented patients), and less frequently had chemotherapy, radiotherapy, hormonal therapy, or biological therapy (all $p < 0.001$), in part because more non-consented patients declined these treatments. They had more often positive tumour margins ($p = 0.05$). However, they did not differ by tumour size, histological type, or hormone receptor status, and tended to have fewer nodes positive. Higher proportions of non-consented patients had missing data on most clinical variables (Table 4). The results of the sensitivity analysis of survival from 90 days, to allow for delayed consent completion up to this time, were very similar.

3.4. Ductal carcinoma in situ (DCIS)

There were also 1642 women with ductal carcinoma in situ (DCIS) disease, of whom 1397 (85.1%) were consented and 245 (14.9%) were not. Mean follow-up was 5.7 years, median 5.2 years and maximum 13.7 years. Survival overall was as expected very high, 96.1% at 5 years for all patients. As with invasive disease, survival for DCIS at each time point and overall was lower in non-consented than in consented patients (Table 1), logrank = 9.8, $p = 0.002$. Survival rates for consented patients were higher than for all patients at all time points, but the differences were less than 1%.

4. Discussion

Cancer registries have been very useful for assessing cancer trends, management, and outcomes. Large national or regional registries may have legislative authority to operate without requiring each patient's consent to be included. However, for clinically based registries, consent of individual patients may be required for data to be stored and to be used for research purposes. Patients who consent may be a selected altruistic group and if so, could give rise to selection biases in analyses. This study uses an opportunity to compare in detail patients who gave informed consent against those who did not.

The clinical registry in this study is probably typical of a registry designed by interested clinicians to bring together the data on patients' demographic, clinical, pathological and treatment details that are already recorded in various hospital records. Outcome data was expanded by regular linkage to the national cancer registry and mortality data done securely by the Ministry of Health using each patient's unique New Zealand national health indicator identifier. Follow-up for mortality is complete unless the patient emigrates and dies outside New Zealand; 'emigration' estimates for this age group are 0.9% per year, but these are overestimates as returns after 16 months' absence are not recorded [6]. The registry had very limited funding. The requirement for informed consent for inclusion on the registry meant that patients were approached by clinical staff usually at their first visit to a

Table 3
Clinical features and treatment of consented and non-consented patients.

		Consented, n = 8282 (%)	Non-consented, n = 962 (%)	p-value
Presentation/ Detection method	Screen detected	3289 (39.8)	301 (31.9)	< 0.0001
	Lump	4663 (56.4)	581 (61.6)	
	Other symptoms	298 (3.6)	33 (3.5)	
	Incidental finding	18 (0.2)	29 (3.1)	
Metastatic disease at diagnosis	Yes	261 (3.2)	114 (13.4)	< 0.0001
	No	7983 (96.8)	740 (86.7)	
Tumour size	< 21mm	4573 (57.1)	468 (57.0)	0.7
	21-50mm	2856 (35.7)	287 (35.0)	
	> 50mm	576 (7.2)	66 (8.0)	
Histological grade	1	1921 (24.1)	217 (27.3)	0.003
	2	3558 (44.7)	375 (47.2)	
	3	2488 (31.2)	203 (25.5)	
Total positive nodes	None	4751 (61.8)	425 (66.0)	0.04
	1-3	1818 (23.6)	148 (23.0)	
	4-9	688 (8.9)	38 (5.9)	
	> 10	435 (5.7)	33 (5.1)	
Histological type	Ductal	6633 (80.1)	751 (78.1)	0.1
	Lobular	950 (11.5)	111 (11.5)	
	Other	699 (8.4)	100 (10.4)	
Estrogen receptor	Positive	6353 (78.3)	682 (78.7)	0.8
	Negative	1765 (21.7)	185 (21.3)	
Progesterone receptor	Positive	5410 (66.6)	575 (66.3)	0.8
	Negative	2708 (33.4)	292 (33.7)	
Surgery	Mastectomy	4304 (52.0)	365 (37.9)	< 0.0001
	WLE/Partial Mastectomy	3645 (44.0)	345 (35.9)	
	No surgery	333 (4.0)	252 (26.2)	
Resection margin (restricted to those who had surgery; N = 8659)	Negative	7314 (93.6)	629 (91.7)	0.048
	Positive	497 (6.4)	57 (8.3)	
Radiotherapy	Yes	5151 (62.8)	385 (41.0)	< 0.0001
	No	2812 (34.3)	506 (53.9)	
	Patient declined	238 (2.9)	48 (5.1)	
Chemotherapy	Yes	2900 (35.6)	153 (16.3)	< 0.0001
	No	4946 (60.7)	733 (77.9)	
	Patient declined	307 (3.8)	55 (5.8)	
Hormonal therapy	Yes	4591 (55.9)	468 (49.6)	0.0004
	No	3366 (41.0)	433 (45.9)	
	Patient declined	256 (3.1)	42 (4.5)	
Biological treatment	Yes	506 (6.2)	30 (3.1)	< 0.0001
	No	7681 (93.3)	917 (95.7)	
	Patient declined	42 (0.5)	11 (1.2)	

Subjects with missing data excluded (see Table 4 for details).

specialist clinic. For some patients the process was delayed but the consent process was completed by first post-surgery therapy, within 90 days of diagnosis. Short delays may have been influenced by the severity of disease, but the analysis of survival from 90 days after diagnosis showed no substantial differences to the main analysis. Patients who did not give consent may have declined it, or may not have been offered the relevant information and consent forms; the data does not distinguish between these.

The results here support other results showing that requiring consent results in only partial participation and this is differential: subjects with more severe disease and worse outcomes tend to be excluded. In this study there was 10.4% non-consent for invasive cancer, resulting in a 2.4% upward bias in 5-year survival if this is based only on consenting patients. Small variations in survival are important: for example, a 2.4% difference is similar to the improvement in breast cancer survival seen over 10 years, between diagnoses in 2000-04 and in 2010-14 in Canada, the US, and Australia [7].

The size of the bias depends on the proportion of patients excluded by non-consent and by how this selection influences this group, which will vary with each registry. Thus, in an observational study of breast cancer in the UK, it was demonstrated that the use of the dataset requiring consent omitted information about many women with locally advanced or metastatic cancer, and also underrepresented women in deprived social groups [8]. A clinical registry of acute renal disease in the US requiring no interventions but requiring informed consent only achieved 52% completeness [9]. A major multicentre effort to record information of the natural history and treatment of stroke in Canada failed because of the requirement for informed consent, so that initially only 39% of eligible patients, and after simplification of the requirements only 50% of eligible patients, give informed consent for the data to be used; and the costs involved in obtaining consent formed a high proportion of the total costs of the endeavour. The authors argued that the avoidance of informed consent from minimal risk observational research is essential [10].

For a planned population-based cohort study of patients with three common cancers requiring further information on therapy and care from eligible patients, only 47% of patients give consent; so while internal comparisons within the group may be valid, the whole group is not, as planned, a representative population-based study [11]. A small study requiring consent from the review of medical records of men with prostate cancer achieved in 84% response rate, but at a considerable cost [12].

Some population groups are particularly difficult to reach. To study unmet needs, in Australia an attempt was made to contact a representative sample of adolescent and young adult survivors of cancer. Initial identification could easily be made from standard existing registries, but an active clinical consent protocol was used by the registries approaching subjects through their clinicians. As a result the overall consent rate was only 7.8%, due mainly to non-responses from clinicians or contact not being established. In contrast very few individuals who were approached refused personal consent [13].

Data completeness has also been threatened on a larger scale. In regions of Germany, law changes in the 1980s requiring informed consent for cancer registries which previously had included all cases of cancer without consent for over 50 years. This quickly resulted in at least 30% failure of registration, and eventual failure of the registries as they were no longer valuable by being incomplete. Subsequent attempts to improve this led to a complicated system using two centres produced duplicate registrations and continued failure [14]. Changes in regulations by large jurisdictions such as the European Union can threaten the completeness or existence of registration and essential linkages [15].

Variations in administrative decisions and ethical committee decisions can threaten registration issues [16]. Even in the same legislative climate, with a common protocol, different organisations can vary greatly on how patients are approached for consent and registration [17]. The efficiency and transparency in the operation of administrative structures and ethical committees also needs considered, particularly if several jurisdictions are involved [18]. It has been noted that “those responsible for framing guidelines on the handling of clinical data and for advising doctors should consider issues related to health surveillance so as public health is not put at risk” [19].

A restrictive policy is not supported by the general public. In a survey of 2872 respondents in the UK in 2005, 95% considered the existence of a national cancer registry with enough detail to assess effectiveness of treatment as useful, and 81% supported legal registration of all cases of cancer to such a registry [20]. Only 16% had any objection to being identified and approached for further study from such a registry.

There is a strong argument that the operation of clinical registries, which require only the information already recorded on hospital and pathology records, and do not involve any direct contact with the

Table 4
Proportions of subjects with missing data.

		Consented, n = 8282 (%)	Non-consented, n = 962 (%)
Ethnicity	Known	7782 (94.0)	906 (94.2)
	Unknown	500 (6.0)	56 (5.8)
Presentation/Detection method	Known	8268 (99.8)	944 (98.1)
	Unknown	14 (0.2)	18 (1.9)
Menopausal status	Known	7940 (95.9)	900 (93.6)
	Unknown	342 (4.1)	62 (6.4)
Tumour size	Known	8005 (96.7)	821 (85.3)
	Unknown	277 (3.3)	141 (14.7)
Histological grade	Known	7967 (96.2)	795 (82.6)
	Unknown	315 (3.8)	167 (17.4)
Total positive nodes	Known	7692 (92.9)	644 (66.9)
	Unknown	590 (7.1)	318 (33.1)
Metastatic disease at diagnosis	Known	8244 (99.5)	854 (88.8)
	Unknown	38 (0.5)	108 (11.2)
Eostrogen receptor	Known	8118 (98.0)	867 (90.1)
	Unknown	164 (2.0)	95 (9.9)
Progesterone receptor	Known	8118 (98.0)	867 (90.1)
	Unknown	164 (2.0)	95 (9.9)
Resection margin (restricted to those who had surgery; N = 8659)	Known	7811 (98.3)	686 (96.6)
	Unknown	138 (1.7)	24 (3.4)
Radiotherapy	Known	8201 (99.0)	939 (97.6)
	Unknown	81 (1.0)	23 (2.4)
Chemotherapy	Known	8153 (98.4)	941 (97.8)
	Unknown	129 (1.6)	21 (2.2)
Hormonal therapy	Known	8213 (99.2)	943 (98.0)
	Unknown	69 (0.8)	19 (2.0)
Biological treatment	Known	8229 (99.4)	958 (99.6)
	Unknown	53 (0.6)	4 (0.4)

patient, should be operated without any requirement for specific consent.

Despite those arguments, legislative and management policies relating to data collection, and the interpretations by individual organisations and by ethics committees, still often require informed consent, even for clinical registries using routine data. This may relate to failure to distinguish between observational work using routine data, which when done by healthcare management as part of routine administration proceeds with little comment, and intrusive research epitomised at the extreme by clinical trials [21]. Traditional medical ethics has its background in the experimental therapies of individual patients, which have guided major ethical initiatives [21]. Clinical trials are valid because the essential comparisons are internal, despite the fact that the subjects involved in a trial may not be representative of the source populations. With registries however, the loss of representativeness caused by a requirement for consent is critical, as a major function of the registries is to provide information on the management and outcome of all patients in a defined population.

It can be argued however that registration itself can be threatening and may be viewed as undesirable [22], in which case a specific consent policy may be appropriate. An opt-out system may be appropriate, as it allows those who feel sensitive to such issues to decline, but in practice very few do, so the remaining database may be representative. Using an opt-out consent system, in Australia an Internet-based database for colorectal neoplasia has been operating with almost 100% completion [23]; and an opt-out system is used to achieve high recruitment for a detailed lung cancer registry [24]. An opt-out system is used for a breast implant registry in the Netherlands, after previous attempts had produced only unreliable and incomplete information [25].

New Zealand like many other countries has a national Cancer Registry, which is based on clinical and pathological data for all patients diagnosed with a first invasive cancer. Such registration is routine and legally protected and there is no requirement for consent. As a result the registry can be complete and can give good information on cancer incidence, and by linkage with mortality data, on survival. However like many large-scale registries the data is extremely limited; for example, little information is collected on extent of disease or stage, treatment, or outcomes such as recurrence. Thus such data is useful background but is inadequate to address many current aspects of cancer management. Clinical registries such as the one described here provide greater detail, and can be operated in conjunction with routine medical records at little additional cost. To be most valuable, such registries need to be population-based and complete, and also need to be linked to other registries, national registries, and to mortality and other hospital data. To operate them efficiently can easily be blocked by inappropriate management or ethical committee decisions.

A registry which uses only the clinical and pathological information already collected and recorded on patients and kept in various places within hospital records should require no explicit consent to gather that data in one place where it can be usefully used for the benefit of all patients. Such is indeed the argument for the existence of national cancer registries without any consent requirement. Any further study requiring access to patients, or further requirements of the patients such as the use of tissues, would require consent and ethical review.

5. Conclusions

Data restricted to patients who give active consent to be included in the patient registry produced a bias in survival results, as the consenting patients are a biased subgroup. In this study, the bias resulted in excluding a group of patients with low survival, and demographic and clinical differences related to this decreased survival. The overall survival rates for invasive cancer up to 10-years are about 2% overestimated if based only on consented patients; while a small difference, this means that survival rates based on all patients are below the 95% lower confidence limits based only on consented patients.. Analyses of clinical and pathological characteristics using only consented patients will also give misleading results. Clinical registries should aim to include all patients, and opt-off consent systems may be appropriate.

Conflicts of interest

The authors declare no conflicts of interest.

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Availability of data and materials

The datasets used in this study contain personal information and are not publicly available, but may be requested from the Auckland Breast Cancer Registry, subject to ethical approvals.

Authors' contributions

VH, MB, and RM developed the concept, and ME, ST, RM and MB analysed the data. All authors contributed to the interpretation of the data and to drafts of the report, and reviewed and approved the submission.

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