Breast cancer survival in Canada and the USA: meta-analytic evidence of a Canadian advantage in low-income areas

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Abstract

Background—This study tested the hypothesis that relatively poor Canadian women with breast cancer have a survival advantage over their counterparts in the USA.

Methods—Seventy-eight independent retrospective cohort (incidence between 1984 and 2000, followed until 2006) outcomes were synthesized. Fixed effects meta-regression models compared women with breast cancer in low-income areas of Canada and the USA.

Results—Low-income Canadian women were advantaged on survival [rate ratio (RR) = 1.14; 95% confidence interval (CI) 1.13–1.15] and their advantage was even larger among women <65 years of age who are not yet eligible for Medicare coverage in the USA (RR = 1.21, 95% CI 1.18–1.24). Canadian advantages were also larger for node positive breast cancer, which may present with greater clinical and managerial discretion (RR = 1.40, 95% CI 1.30–1.50), and smaller when Hawaii, the state providing the most Canadian-like access, was the US comparator (RR = 1.12, 95% CI 1.01–1.20).

Conclusions—More inclusive health care insurance coverage in Canada vs the USA, particularly among each country's relatively poor people, seems the most plausible explanation for such Canadian advantages. Provision of health care for all Americans would likely prevent countless early deaths, particularly among the relatively poor.

Keywords

Breast cancer; socio-economic factors; place; survival; node positive breast cancer; meta-analysis; health insurance; single payer; Canada; USA

The CONCORD study's worldwide population-based analysis estimated that the USA and Canada, respectively, rank number one and two at the top of the world's breast cancer survival distribution, and that the overall difference between them may be fairly characterized as miniscule [5-year relative survival rate ratio (RR) = 1.02; 95% confidence interval (CI) 1.00–1.04].[1] The first observational study to specifically compare Canada with the USA on this sentinel health outcome also observed an extremely small breast cancer survival advantage among US women.[2] However, neither of these studies accounted for

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socio-economic factors in any way. The first study to do so hypothesized and found an income-by-country interaction.[3] Based on a health insurance theory, it observed a relatively large survival advantage among low-income women with breast cancer in a large Canadian metropolitan area (Toronto, Ontario) as compared with their US counterparts in Detroit, Michigan (RR = 1.30, 95% CI 1.23–1.38). Its null findings were equally interesting. No between-country survival differences were observed among its middle-or high-income groups. It suggested that more equitable access to Canada's single payer health care system was the most plausible explanation for its pattern of findings.

This field's health insurance theory developed over time through key sub-cohort comparisons. For example, it was hypothesized that the observed Canadian survival advantage ought to be even larger among low-income women, <65 years of age, who are not yet eligible to participate in the USA's Medicare program. This age-stratified hypothesis was affirmed with other Canadian and US metropolitan samples.[4,5] Such advantaged Canadian health outcomes are consistent with the findings of two recent systematic reviews. [6,7] Though their scopes were larger than breast cancer survival, they both included five such Canadian–US comparative studies, and they provided sound empirical direction for this meta-analysis. Both reviews identified significant study outcome heterogeneity that they were not able to adequately explain, and they respectively suggested that future analyses ought to account for disease stage at diagnosis and geographic diversity. Extending previous analyses with the most contemporaneous studies that now include staged and unstaged samples as well as samples of large urban to rural places, this meta-analysis did so. It hypothesizes a Canadian breast cancer survival advantage compared with the USA among the relatively poor and an even larger advantage among relatively poor women <65 years of age. It will also exhaustively explore clinical, contextual and methodological study variability.

Methods

Selection of studies

MEDLINE was searched in September of 2008 on the following key word scheme: breast cancer and survival and Canada and the USA. This search for published research literature was augmented with conceptually similar searches for unpublished research reports: *Digital Dissertations*, world wide web searches and personal contact with key informants within this field's scholarly network. Additionally, studies had to meet these inclusion criteria: (i) their within- and between-country comparisons integrated socio-economic factors and (ii) their analytic models minimally adjusted for within- and between-country age differences. Eight studies were so selected.[3–5,8–12] Socio-economic status (SES)–breast cancer survival associations that were observed among different age cohorts in different places were treated as independent hypotheses. A total of 78 such independent study outcomes (within- or between-country comparisons) were included in this meta-analysis and summarized within seven hypothetical domains, each tested among all adult and younger adult (<65 years of age) samples. These included breast cancer survival in middle-income areas compared with high-income areas within-Canada and within the USA, low-income areas compared with high-income areas within-Canada and within the USA, and the survival of Canadian women

with breast cancer compared with their US counterparts, each within relatively high- middle-
or low-income areas.

Meta-analysis

This meta-analysis adhered closely to the analytic plan seminally outlined by Greenland.[13]
Age-adjusted survival rate ratios (RRs) estimated primary study relative risks. Fixed and
random effects meta-analytic models were initially explored for pooling RRs, and their
pooled estimates typically differed by only a few hundredths of a decimal place.
Heterogeneity of RR distributions within the 14 domains of meta-analytic interest was also
explored. Most of them (11 of 14) were not significantly heterogeneous. Therefore, this
meta-analysis used fixed effects models that assume substantial homogeneity of effects
within specific categories of interest. Natural logarithms of study RRs were weighted by
their inverse variances, computed from standard errors ($1/SE^2$) so that larger, more precise
studies weighed more. Standard errors were estimated from study statistics, generally from
reported 95% CIs. Such precision-weighted effects were then pooled within the 14 domains
of interest using weighted regression models. Pooled RRs within 95% CIs were calculated
from regression statistics, as were tests of heterogeneity within pooled groups (χ^2) and
comparisons between groups (z).[13,14] If significant heterogeneity was observed ($P < 0.05$),
its possible sources—contextual, clinical and methodological—were examined through
subgroup analyses. Certain subgroups were determined *a priori*. That is, at least one of the
primary studies suggested their significance and direction. For example, SES–survival
associations may be larger in province-wide analyses than in more specific places, and
Canadian–US survival differences in low-income areas may be larger for node positive
breast cancer, but smaller when the US context is Hawaiian or when area median annual
household income is used, rather than low-income or poverty measures of SES. The
potential moderating affects of other study characteristics were explored: incident cohort
dates, urban or rural, racial/ethnic sample composition, city size, survival measurement
(observed all-cause or cancer-specific), SES quantiles (tertiles, quintiles or deciles) and
length of follow-up. Study characteristics were abstracted independently from full primary
study manuscripts by two coders. After discussion and resolution of non-systematic
discrepancies, their agreement was 100%.

Results

Sample description

All of the eight included studies were large, cancer registry-based, retrospective cohorts
(ranging from 1789 to 74 949 participants, median = 7888; Table 1). The aggregate
population-based meta-analytic sample was 130 083 women with invasive breast cancer that
was diagnosed, for the most part, in the mid-1980s to the early 1990s and followed until the
mid- to late-1990s. One cohort of women with breast cancer was diagnosed between 1998
and 2000 and followed until 2006. All of the cohorts were followed for 5 years, except for
one that was variably followed it seems for 2–5 years. Five of the studies restricted their
samples to large metropolitan areas. In each of these, Toronto, Ontario was compared with
various US cities: Detroit (three studies), Honolulu, Hawaii and an aggregation of San
Francisco, California–Seattle, Washington–Hartford, Connecticut in another. One study

focused on smaller urban areas (Winnipeg, Manitoba and Des Moines, Iowa) and two studies compared the province of Ontario with the state of California or the USA as a whole. The provincial state study purposively sampled diverse places (large to small urban and rural places) while the provincial national study included the population of women with breast cancer in Ontario and a Surveillance, Epidemiology and End Results (SEER) program-based US sample. Such contextual variability represents meta-analytic opportunities to better understand Canadian–US differences in breast cancer care.

All of the eight studies were ecological with respect to SES measurement. Most of the income measures were based on census tracts (CTs). One used enumeration areas (somewhat smaller urban populations than CTs) and two used census subdivisions (somewhat larger rural populations than CTs). Seven studies used measures of low-income (Canada) and poverty (USA) prevalence and two used measures of median household income (one study used both). All of the studies accounted for age distribution differences within- and between-countries, but only one accounted for case-mix differences on the stage of disease at the time of diagnosis. Finally, all of the studies' outcomes were of observed survival (four all-cause and four cancer-specific). Again, such methodological variability presents meta-analytic opportunities to better understand Canadian–US differences in breast cancer care and outcomes.

Pooled SES–breast cancer survival associations

Within-country SES–survival gradients—SES was not strongly related to breast cancer survival in most of the Canadian contexts studied. Three of the four pooled within-Canada RRs displayed in Table 2 were null. Even studies that compared women with breast cancer in the lowest-income quantiles, observed very little overall survival disadvantage among them compared with those in the highest-income areas (RR = 0.94, 95% CI 0.93–0.95). This distribution was significantly heterogeneous though. As expected, income–survival associations were larger in province-wide analyses (two outcomes) than in specific urban or rural places (seven outcomes), respectively (RR = 0.80, 95% CI 0.78–0.82) and (RR = 0.99, 95% CI 0.98–1.00). The specific places were largely represented by greater metropolitan Toronto, but one small city (Windsor, Ontario) and a rural Ontario sample were also represented. The affect of income on breast cancer survival seems not to be homogeneously experienced across Ontario's diverse places. Clearly in some places such as Toronto during the mid-1980s to the mid-1990s, there seems to have been no such relationship, but in other places, not specifically identified yet, a modest relationship must have existed.

On the other hand, SES did seem to be consistently and strongly related to breast cancer survival across all of the US contexts studied. All of the four pooled within-US RRs displayed in Table 2 were notable. Moreover, among all adult and younger adult US samples, meta-analytic trends, suggestive of a causal income–survival relationship, were observed. That is, survival among women with breast cancer in middle-income areas was lower than that observed among their counterparts in the highest-income areas, and survival among such women in the lowest-income areas was incrementally lower than that observed in middle-income areas. In terms of practical policy or public health importance, studies that

compared women with breast cancer in the USA's lowest-income areas with those in its highest-income areas, observed a very large survival disadvantage among relatively low-income women (RR = 0.73, 95% CI 0.72–0.74). Overall, their risk of dying, most typically within 5 years of being diagnosed, was nearly 30% greater than the risk experienced by relatively high-income women. Given the prevalence of breast cancer over the life course of women in the USA, this could represent a huge additional population-level risk among poor women.

Between-country hypothesis tests—Respective, null and trivial Canadian–US breast cancer survival differences were observed in the highest- and middle-income areas. But as hypothesized, in the lowest-income areas studies, Canadian women were advantaged (RR = 1.14, 95% CI 1.13–1.15), and this advantage was even larger among younger women, not yet eligible for Medicare in the USA (RR = 1.21, 95% CI 1.18–1.24). Both of these effect distributions were more heterogeneous than would be expected due to sampling variability alone and both of their pooled effects were moderated as expected by stage of disease and place (Table 3). Canadian–US survival differences in low-income areas were larger for node positive breast cancer, and they were smaller when the state studied was Hawaii. The observed relative US disadvantage seemed particularly large among younger women, not yet eligible for Medicare, with node positive breast cancer (RR = 1.40, 95% CI 1.30–1.50). Low-income patients in the USA may be much more disadvantaged than their Canadian counterparts at the hands of the greater clinical and managerial discretion (surgical and adjuvant innovations of varying costs and evidentiary supports) that has attended the contemporary treatment of node positive breast cancer. After age, disease stage and place were accounted for, no other contextual or study methodological characteristic could further explain study outcome variability.

Discussion

This study found that women with breast cancer who live in low-income areas of the USA were disadvantaged on 5-year survival compared with their Canadian counterparts. Moreover, US women <65 years of age who are not yet Medicare eligible were even more disadvantaged. US breast cancer survival disadvantages were also larger for node positive breast cancer and in states where the prevalence of the uninsured was relatively higher. Along with the consistent and relatively large direct income–survival gradients observed among US samples, all of the between-country meta-analytic findings were consistent with the health insurance theory that is at the center of this field's inquiry. Moreover, its between-country ecological findings have been convergently validated by recent within-USA studies that have consistently observed very strong relationships between various under- and uninsured statuses, measured at the individual level, and relatively later stage at breast cancer diagnosis, lack of treatment access and early death.[15–18] This study's findings were also consistent with a recent, but as of yet unpublished, California–Ontario study that found that low-income Canadian women with breast cancer gained greater access to adjuvant radiation therapy, and contrary to common wisdom, experienced treatment delays that were no different than those of their US counterparts. Canada's single payer health care system seems to provide much more equitable breast cancer care than does the USA's multiple

payer system. The Canadian system's most pronounced evidence-based advantage is clearly among the relatively poor who typically experience much better breast cancer outcomes in Canada than in the USA.

Lack of health insurance vs alternative explanations

A number of possible alternative explanations have been advanced by opposing theorists: (i) there is a wider economic divide between the relatively rich and poor in the USA; (ii) there are greater disadvantages associated with being a member of a racial/ethnic minority group in the USA; (iii) Canadians are advantaged in lifestyle and life expectancy; and (iv) Canadian women may merely be diagnosed earlier, any observed breast cancer care and outcome advantages only being apparent, the result of lead time bias, rather than of any systemic Canadian health care advantage.[5] This meta-analysis' systematic replications across diverse contexts and methods provided robust rejoinders to essentially rule out such alternative explanations. Canadian breast cancer survival advantages were observed across diverse Canada–USA comparisons, including those in which the income divide was demonstrably wider in the Canadian sample (Winnipeg, Manitoba vs Des Moines, Iowa). The Canadian advantage was consistently observed across racially/ethnically diverse US samples, including comparisons with samples prevalently represented by African American (Detroit), Asian American (San Francisco) and Hispanic (Modesto, California) women. This meta-analysis could not adjust for this factor as Canadian cancer registries do not code race/ethnicity. A number of the reviewed studies, however, did replicate key findings with the following conservative low-income area comparison: non-Hispanic white women in the USA vs the entire diverse sample of Canadian women.[3,4] The age-adjusted, all-cause Canadian survival advantage was validated with cancer-specific survival analyses that accounted for competing causes of death. Finally, stage-adjusted analyses effectively ruled out lead time bias as a potent alternative explanation. In fact, the even larger Canadian survival advantage observed among low-income women with node positive breast cancer, a presentation that tends to maximize clinical and managerial discretion, only served to further indict the US health care system.

This meta-analysis could conceivably be limited by its combining all-cause and breast cancer-specific study outcomes. For the following reasons it probably was not. First, all-cause vs cancer-specific survival outcomes did not moderate this review's within- or between-country main effects. Secondly, though length of survival is highly accurate in US cancer registries, the underlying cause of death is not.[19] Therefore, this review's systematic replication of cancer-specific with all-cause findings served to bolster confidence in review inferences related to overall population cancer burdens. Next, cancer is the underlying cause of death among the vast majority of women with cancer,[4,5] and the underlying cause of many 'non-cancer' deaths can often be directly associated with non-treatment or even with some cancer treatment complications.[20] Finally, one primary study sub-analysis, limited to women <50 years of age seemed to rule out such methodological confounding.[11] Their expected survival without cancer was virtually 100% and their underlying cause of death was nearly exclusively cancer. Within-and between-country findings were systematically replicated among them.

Though its sampling frame included unpublished sources, this meta-analytic sample ultimately included only published studies. One may legitimately wonder if publication bias could be a potent alternative explanation for its findings. It seems probably not for the following reasons. First, this review's meta-analytic hypotheses predicting advantaged Canadian survival specific to low-income areas and specific to younger women were not the primary hypothetical concerns of some of its included studies. Also, most of the primary studies were not designed to test the specific effect modifiers that this meta-analysis did (node positive vs node negative disease or Canadian comparisons with Hawaii vs other states). Secondly, of the 14 domains studied (Table 2), eight of their pooled RRs were null or practically null. Those are precisely the sort of findings one would not readily expect to retrieve from published reports if publication bias, that is, a preference to publish so-called significant findings, were potent. It seems highly improbable that publication bias could account for such a complex pattern of pooled null effects along with key pooled 'significant' main and moderator effects.

Relatedly, the robustness of this meta-analytic review's sample was tested with a number of sensitivity procedures. First, the sampling scheme produced eight large, cancer registry-based, retrospective cohort studies that were quite methodologically homogeneous. Secondly, ecological measurement variability was not associated with study outcome variability. Thirdly, fixed and random effects models were near exact replicates of each other. Fourthly and finally, none of the pooled main effects changed appreciably with the exclusion of the relative risk estimate that was based on the smallest study sample. It seems quite clear that no single study alone drove any of this meta-analysis' pooled effects.

Future research needs

Not surprisingly, as no US cancer registry routinely collects socio-economic data, all of the studies included in this meta-analytic review were ecological with respect to the measurement of SES. The construct and predictive validities of the most prevalent low-income, typically CT-based measures have been well established in US contexts.[21–23] However, even the most extremely low-income areas represented among the US samples included in this review were only in the range of 20–25% poor. Such neighbourhoods were substantially less impoverished than the extremely vulnerable, concentrated poverty neighbourhoods where >40% of the households were poor and were the focus of Jargowsky's validation.[21] Such extremely poor neighbourhoods have not been specifically studied in this field. Future study in these most vulnerable of USA neighbourhoods would be of great human and scientific interest and policy importance.

This field has used two conceptual measures of SES, both ecological that principally describe CTs: the prevalence of low-income households in each CT and CT median household income. In Canadian contexts, however, the relative predictive validity of these two SES measures has been debated.[12,24] It is important to note that such measurement variability did not confound this review's central hypothesis related to advantaged Canadian survival in low-income areas. It relates though to the interpretation of this review's within-Canada descriptive findings. Consistent with a recent study of median neighborhood income and endometrial cancer survival in Ontario,[25] this review found that SES did not seem to be

related to breast cancer survival in most of the Canadian contexts studied. The few included province-wide analyses suggested that income–survival gradients probably do exist somewhere in the province. These reviewed studies did not identify where such gradients might exist, but another recent median income-based analysis of breast cancer survival in Ontario suggested that they may, in fact, be restricted to certain small cities with less than adequate health care service endowments.[26] This study, however, did not have sufficient meta-analytic power to adequately resolve these issues. Notwithstanding the typical worldwide robustness of the SES–cancer survival relationship to various definitions of SES, [27] studies that advance our Canada-specific understandings of their construct and predictive validities are needed. They would further enable our ability to practically interpret this field's equivocal SES–breast cancer survival gradients, from null to modest across Canada's diverse places.

Conclusion

This study found consistent evidence that women with breast cancer who live in low-income areas of the USA are considerably less likely to survive for 5 years than are their Canadian counterparts, whereas, such women who, respectively, reside in the middle- and high-income areas of each country do not practically differ. It robustly affirmed a health insurance theory to explain this pattern. More inclusive health care insurance coverage in Canada vs the USA, particularly among each country's relatively poor people, seems the most plausible explanation for such a Canadian advantage. Provision of health care for all Americans would likely prevent countless early deaths from breast cancer and other common diseases, particularly among the poor. As it sentinels caution against policies that would further privatize and thus add payer tiers to the Canadian health care system, this study suggests that US policy makers probably have much to learn from their counterparts to the north.

KEY MESSAGES

- The association of neighbourhood-level SES with breast cancer survival is much stronger in the USA than it is in Canada.

- Low-income Canadian women with breast cancer are more likely to survive for 5 years after their diagnosis than are similarly poor women with breast cancer in the USA.

- Younger low-income Canadian women with breast cancer are even more advantaged as compared with their US counterparts who are not yet eligible for Medicare.

- More inclusive health care insurance coverage in Canada seems the most plausible explanation for such consistently observed Canadian advantages.

Acknowledgments

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Table 1

Description of the eight studies of female breast cancer survival included in the meta-analysis

Reference[3-5,8-12]	Sampling frame				Socio-economic measure				Survival Measure
	Canadian and US places	Cohort incidence years	Followed until	Aggregate sample	Unit	Conceptual definition	Groups[d] compared		
Gorey et al. 1997	Toronto vs Detroit	1984–1988	1994	8186	CT	Low-income Prevalence	Tertiles		5-year Cancer-specific
Gorey et al. 2000	Toronto vs Hololulu	1986–1990	1996	7590	CT	Low-income Prevalence	Deciles		5-year All-cause
Gorey et al. 2003	Winnipeg vs Des Moines	1984–1992	1998	3928	CT	Low-income Prevalence	Quintiles		5-year All-cause
Boyd et al. 1999	Ontario vs USA[a]	1987–1992	1995	74 949[c]	CT, EA and CSD	Mdn Income	Quintiles		2- to 5-year Cancer-specific
Gorey et al. 2000	Toronto vs San Francisco, Seattle, Hartford	1986–1988	1994	9748	CT	Low-income Prevalence	Tertiles		5-year All-cause
Gorey et al. 1998	Toronto vs Detroit	1986–1988	1994	1789	CT	Low-income Prevalence	Quintiles		5-year Cancer-specific
Gorey et al. 2009	Ontario[b] vs California[b]	1998–2000	2006	1923	CT and	Low-income Prevalence	Quintiles		5-year All-cause
Zhang-Salomons et al., 2006	Toronto vs Detroit	1988–1993	1999	21 970	CT	Low and Mdn Income	Quintiles		5-year Cancer-specific

Note. CT, census tract; EA, enumeration area; CSD, census subdivision; Mdn, median. All adult samples were 20–25 years of age. Three studies additionally analysed younger/older groups (<65/65+). 4,5,11 One study analysed staged groups (node negative/positive breast cancer).[11]

[a]SEER program based.

[b]Respectively, sampled large metropolitan areas (greater metropolitan Toronto and the San Francisco Bay area), smaller cities (Windsor and Modesto) and rural places in both Ontario and California.

[c]Sample not reported. Estimated by secondary analysis.

[d]Most extreme comparison used in each study.

Table 2

Summary of income–breast cancer survival associations

| Comparisons | Within-country | | Between-country |
	Canada	USA	Canada/USA
Adult samples: 25 years[a]			
Highest-income areas			
Study outcomes	NA	NA	6
Total participants	NA	NA	5436
RR range	NA	NA	0.91–1.04
Pooled RR (95% CI)	1.00	1.00	0.99 (0.97,1.01)
Middle-income areas			
Study outcomes	7	7	6
Total participants	9743	5148	4845
RR range	0.93–1.04	0.90–1.00	1.02–1.07
Pooled RR (95% CI)	1.00 (0.98,1.02)	0.96 (0.94,0.98)	1.03 (1.01,1.05)
Lowest-income areas			
Study outcomes	9	9	10
Total participants	40 918	27 056	30 207
RR range	0.80–1.02	0.53–0.96	0.99–1.30
Pooled RR (95% CI)	0.94[b] (0.93,0.95)	0.73 (0.72,0.74)	1.14[b] (1.13,1.15)
Younger adult samples: <65 years			
Highest-income areas			
Study outcomes	NA	NA	3
Total participants	NA	NA	3112
RR range	NA	NA	0.92–0.99
Pooled RR (95% CI)	1.00	1.00	0.98 (0.95,1.01)
Middle-income areas			
Study outcomes	2	2	3
Total participants	3008	1183	2564
RR range	0.98–0.99	0.82–0.93	1.02–1.11
Pooled RR (95% CI)	0.99 (0.96,1.02)	0.88 (0.84,0.92)	1.03 (1.00,1.06)
Lowest-income areas			
Study outcomes	3	5	6
Total participants	3105	1691	2708
RR range	0.95–1.01	0.69–0.88	1.12–1.43
Pooled RR (95% CI)	1.00 (0.98,1.02)	0.80 (0.77,0.83)	1.21[b] (1.17,1.25)

Note. Sensitivity analyses found that none of the pooled RRs changed appreciably with exclusion of the RR that was based on the smallest study sample.

[a] One study sampled women 20 years of age.

[b] Distribution significantly heterogeneous (χ^2-statistic), $P < 0.05$.

Table 3

Summary of income–breast cancer survival associations moderated by stage at diagnosis and place: disaggregation of heterogeneous between-country comparisons in low-income areas

	Stage at diagnosis		US places	
	Node positive	**Unstaged**	**Hawaii**	**Other**
Adult samples: 25 years				
Study outcomes	1	9	2	7
Total participants	193	30 014	3321	26 693
RR (95% CI)	1.22 (1.02,1.46)	1.13 (1.12,1.14)	1.07 (1.05,1.09)	1.16 (1.15,1.17)
Younger adult samples: <65 years				
Study outcomes	2	4	1	3
Total participants	183	2525	1470	1055
RR (95% CI)	1.40 (1.30,1.50)	1.18 (1.15,1.22)	1.12 (1.01,1.20)	1.24 (1.20,1.29)

Notes. Each paired comparison within age categories—node positive vs unstaged or Canada–USA comparisons that used Hawaiian vs other US samples—was significantly different (z), $P < 0.05$. Each paired comparison between age categories (e.g. node positive breast cancer among women 25 years of age vs node positive breast cancer among women <65 years of age) was significantly different (z), $P < 0.05$.