

# An international comparison of male and female breast cancer incidence rates

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Global international trends in female breast cancer incidence have been described previously but no comparable analysis of male breast cancer incidence rates has been conducted. We obtained male and female case and population data using Cancer Incidence in Five Continents (CI5). We calculated age-adjusted, sex-specific incidence rates and female-to-male incidence rate ratios (FMIRRs) and compared trends of such for the period 1988–2002. This analysis included 8,681 male breast cancer cases and 1.14 million female breast cancer cases. The highest male incidence rate was observed in Israel at 1.24 per 100,000 man-years, and the highest female incidence rate was observed in the United States at 90.7 per 100,000 woman-years. The lowest incidence rates for males (0.16) and females (18.0) were observed in Thailand. In general, male breast cancer incidence trends were variable; a minority of countries displayed evidence for an increase. In contrast, female incidence rates have been increasing in a majority of countries. The Pearson correlation coefficient ( $r$ ) for male and female breast cancer incidence rates by country during 1988–2002 was 0.69. Male breast cancer rates were generally less than 1 per 100,000 man-years, in contrast to the much higher rates of female breast cancer, providing for an overall FMIRR of 122. The differences in both incidence rates and time trends between males and females may reflect sex differences in underlying risk factors, pathogenesis, and/or overdiagnosis. Conversely, the high correlation between male and female breast cancer incidences may indicate that both sexes share some common risk factors for breast cancer.

The vast majority of cancer types have a higher incidence rate in males relative to females,<sup>1</sup> with one of the few and obvious exceptions to the rule being breast cancer. It is estimated, for example, that 229,060 people will be diagnosed with breast cancer in the United States in 2012, with less than 1% of these cases appearing in men.<sup>2</sup> Breast cancer has traditionally been considered a female-specific disease, and lack of awareness of its occurrence in men may lead to diagnoses at later age and more advanced stage than in females.<sup>3</sup>

**Key words:** breast neoplasms, sex, incidence, trends, epidemiology, male, female

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A previous analysis using cancer incidence data from the US Surveillance, Epidemiology and End Results (SEER) databases examined male breast cancer and compared this with female breast cancer.<sup>4</sup> Similar breast cancer incidence trends among males and females were interpreted to suggest the existence of common breast cancer risk factors that influence both sexes. Although the evidence is equivocal as to whether men diagnosed with breast cancer have a worse prognosis, cancer-specific survival, and overall survival, compared with female breast cancer cases,<sup>3,5–8</sup> recent histopathologic<sup>5,9,10</sup> and molecular<sup>11–13</sup> studies are persuasive to the thesis of heterogeneity in pathogenesis of disease by sex. In recent years, there has been an increasing number of epidemiologic studies of male breast cancer, and we are slowly unraveling the risk factor profile of this rare disease.<sup>14–17</sup> To aid hypotheses and direction of such research, we undertook the first international comparison of female and male breast cancer incidence rates using data from Cancer Incidence in Five Continents (CI5) to evaluate sex-specific incidence trends as well as incidence rate ratios for the period 1988–2002.

## Material and Methods

Data were provided by the International Agency for Research on Cancer (IARC) and were derived from CI5 Volumes I–IX (1958–2002).<sup>18</sup> Female and male breast cancer case counts and their corresponding populations, in single calendar years, were obtained for each of 18 age groups (0–4, 5–9, . . . , 80–84, 85+) for 88 registries of various ethnic groups in the

**What's new?**

Are the causes of breast cancer in men similar to those in women? Is male breast cancer a different disease entity, or is it the same in men and women? In this study, the authors have compiled the first epidemiologic analysis comparing international trends for male and female breast-cancer incidence. They conclude that, while incidence patterns are similar, there may also be sex-specific processes that play a role in the pathogenesis of this disease.

Americas, Europe, Asia and Oceania. We grouped these registries by country to enable calculation of sex-specific, age-standardized incidence rates for each of 25 countries for up to nine consecutive 5-year calendar periods (1958–1962, 1963–1967, ..., 1998–2002). A listing of registry and time period coverage for each country is included in Table 1. Incidence rates per 100,000 man or woman-years were age-adjusted to the World Standard Population.<sup>19,20</sup> The female-to-male incidence rate ratio (IRR) was calculated using the female age-adjusted incidence rate as the numerator and the male age-adjusted incidence rate as the denominator. Ninety-five percent confidence intervals for the female-to-male IRRs and sex-specific incidence rates were estimated for each 5-year calendar period as well as the total combined period for each country, according to the method of Tiwari *et al.*<sup>21</sup>

In each of the male and female data extractions, populations for age group 85+ or both age groups 80–84 and 85+ were collapsed into the preceding age group in several registries from developing countries. Consequently, incidence rates were age-adjusted in 5-year categories (0–4, 5–9, 10–14 years, *etc.*) with the final category being ages 75+ years; the world standard population weight for the age group 75+ years was calculated by summing the weights for the age groups 75–79, 80–84 and 85+. The starting year in which data were available varied by registry, thereby reducing periods of coverage for certain countries from the maximum possible of 45 years (see Table 1 for details). Cancer incidence data for the period 1988–2002 were available from at least one registry for each country included in this analysis, thus these years constituted the primary analytic period. The number of registries and period covered by each respective registry varied by country. Countries for which data were restricted to regions or ethnicities are presented in italic font in tables and figures.

International trends in male and female breast cancer incidences were assessed, tabulated and plotted for the period 1988–2002. Estimated annual percentage changes (EAPCs) were estimated by fitting a least squares regression to the natural logarithm of rates based on 3-year groupings for the period 1988–2002, with 95% confidence intervals calculated using the *t*-distribution.<sup>22</sup> Sex-specific incidence rates were also evaluated stratified by age group (<50 and ≥50 years) and by the three most recent 5-year calendar periods (1988–1992, 1993–1997 and 1998–2002). Countries with the highest male breast cancer incidence rates during the period 1958–2002 were graphed separately with female breast cancer incidence rates and male-to-female IRRs for further investigation. Additional analyses were conducted which assessed the corre-

lations between male and female breast cancer incidence rates, and between sex-specific breast cancer rates and health expenditure per capita for the year 2000.<sup>23</sup> Incidence rates were also stratified by health expenditure per capita. We also compared sex-specific breast cancer incidence rates and female-to-male IRRs for periods pre- (1978–1982) and post- (1998–2002) introduction of national screening programs for women. For this analysis we selected all countries that had introduced a national screening program prior to 1996 (Refs. 24–28) as to allow time for implementation to assess the effects of such on incidence rates during 1998–2002. Of the countries available for analysis, only Columbia and Poland did not have a national screening program *and* were considered to be relatively unaffected by opportunistic screening prior to 2003, and only Poland had cancer incidence data for the period 1978–1982. Thus Poland was also assessed in this subgroup analysis as a “negative control.” Stata (Stata Corp. LP, 2011, release 11.2) was used for data processing and analysis, and SigmaPlot (Systat Software, 2008, version 11.0) was used to produce graphs.

**Results**

Table 2 shows overall sex-specific, age-adjusted incidence rates and female-to-male IRRs for the period 1988–2002 for each country, as well as their respective 95% confidence intervals. The highest female breast cancer incidence rates occurred in the United States (90.7 per 100,000 woman-years), and the lowest rate was seen in Thailand (18.0). Breast cancer incidence in males was highest in Israel (1.24 per 100,000 man-years) and lowest in Thailand (0.16). The female-to-male IRR was highest in Singapore (205) and lowest in the Philippines (55). Variability in the IRR values did not appear to be explained by continent. As can be seen from the EAPCs, female breast cancer incidence rates have increased for all countries included in this analysis. This was statistically significant for 18 of the 25 countries assessed (Table 2), while consistent trends across 5-year time periods were observed for 21 of the 25 countries (Supporting Information Table 1). Of particular note are the EAPCs for Thailand (4.17), Singapore (3.47), Costa Rica (3.25) and Brazil (3.21). Conversely, in our assessment of male breast cancer incidence rates there appeared to be much less consistency in trends across the 5-year periods displayed—nine (Philippines, Austria, Denmark, Estonia, Poland, Spain, UK, Canada and Australia) of the 25 countries presented consistent patterns (Supporting Information Table 1). EAPCs indicated that the greatest increases in incidence were in Austria (12.04), Brazil (10.45) and Costa Rica (5.47), while the

**Table 1.** Registries and time periods available for analysis

Country	Region	Time Period
Australia	Australia, New South Wales	1983–2002
	Australia, South	1978–2002
	Australia, Tasmania	1978–2002
	Australia, Victoria	1983–2002
	Australia, Western	1983–2002
Austria	Austria, Tyrol	1988–2002
Brazil	Brazil, Goiania	1988–2002
Canada	Canada, Alberta	1973–2002
	Canada, British Columbia	1978–2002
	Canada, Manitoba	1958–2002
	Canada, New Brunswick	1978–2002
	Canada, Nova Scotia	1978–2002
	Canada, Prince Edward Island	1983–2002
	Canada, Newfoundland	1978–2002
	Canada, Ontario	1978–2002
	Canada, Saskatchewan	1968–2002
Colombia	Colombia, Cali	1983–2002
Costa Rica	Costa Rica	1983–2002
Denmark	Denmark	1978–2002
Ecuador	Ecuador, Quito	1988–2002
Estonia	Estonia	1968–2002
France	France, Bas-Rhin	1978–2002
	France, Calvados	1978–2002
	France, Doubs	1978–2002
	France, Haut-Rhin	1988–2002
	France, Hérault	1988–2002
	France, Isère	1979–2002
	France, Somme	1983–2002
	France, Tarn	1983–2002
	Iceland	1958–2002
	India	1978–2002
India	India, Mumbai	1978–2002
	India, Chennai	1983–2002
Israel	Israel: Jews	1963–2002
Italy	Italy, Florence	1985–2002
	Italy, Parma	1978–2002
	Italy, Ragusa Province	1983–2002
	Italy, Romagna	1988–2002
	Italy, Torino	1985–2002
	Italy, Lombardy, Varese province	1978–2000 <sup>1</sup>
Italy	Italy, Modena	1988–2002
	Japan	1978–2002
Japan	Japan, Miyagi Prefecture	1978–2002
	Japan, Osaka Prefecture	1963–2002
Netherlands	The Netherlands, Eindhoven	1973–2002

**Table 1.** Registries and time periods available for analysis (Continued)

Country	Region	Time Period
Philippines	Philippines, Manila	1983–2002
Poland	Poland, Cracow City	1978–2002
	Poland, Warsaw city	1988–2002
Singapore	Singapore: Chinese	1968–2002
	Singapore: Malay	1968–2002
Slovakia	Slovakia	1973–2002
Spain	Spain, Granada	1985–2002
	Spain, Murcia	1983–2001 <sup>1</sup>
	Spain, Navarra	1973–2002
	Spain, Tarragona	1983–2001 <sup>1</sup>
Spain	Spain, Zaragoza	1978–2000 <sup>1</sup>
	Switzerland	1973–2002
Switzerland	Switzerland, Geneva	1973–2002
	Switzerland, St Gall-Appenzell	1983–2002
Thailand	Thailand, Chiang Mai	1983–2002
UK	UK, England, Merseyside and Cheshire	1978–2002
	UK, England, North Western	1979–2002
	UK, England, Oxford	1985–2002
	UK, England, Birmingham & West Midlands Region	1979–2002
UK	UK, England, Yorkshire	1983–2002
	UK, Scotland	1978–2002
USA	USA, SEER (9 registries)	1978–2002

<sup>1</sup>Time period ends before 2002. Italicized country names indicate data are regional or restricted by ethnicity.

greatest decreases were in Australia (−3.38), Poland (−2.28) and Singapore (−1.96). However, it should be noted that EAPC confidence intervals for male breast cancer incidence trends were wide, a factor attributable to the small numbers of cases that accrue each year of this rare disease.

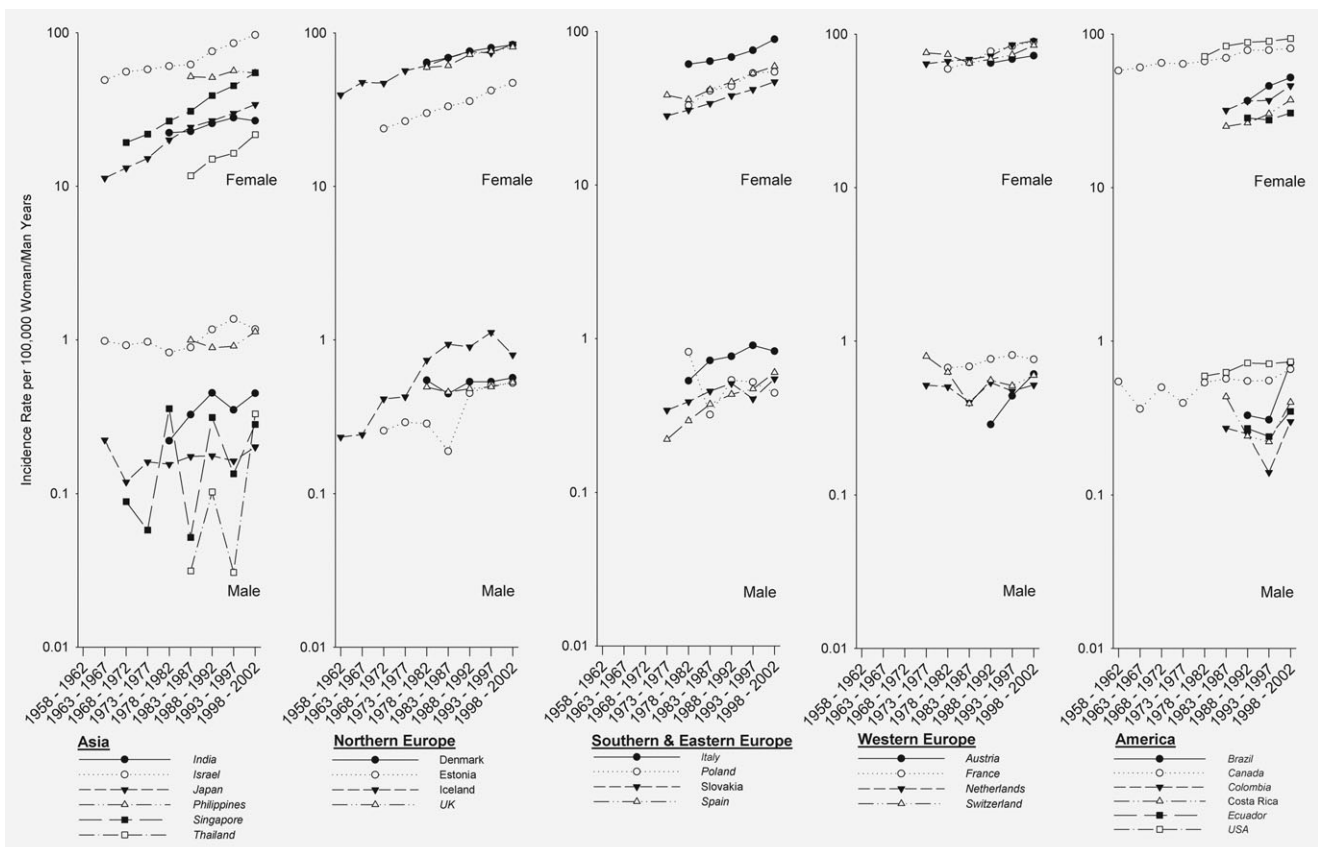
Figure 1 depicts trends in female and male breast cancer incidences for each continent (except Oceania) by country for the full period of analysis (1958–2002) for all ages. For a majority of countries, male breast cancer incidence trends are either difficult to discern, due to volatility attributable to small numbers (Singapore and Thailand), or show some evidence of an increase (India, Iceland, Italy, Spain and Brazil). However, even those countries which indicate an increase, caution is warranted as these rates are still based on small numbers. Female breast cancer rates appear to be steadily increasing over time regardless of continent. Countries that have high or low female breast cancer incidence rates tend to have correspondingly high or low male breast cancer incidence rates. In Northern Europe, the lowest female breast cancer incidence rates and lowest male breast cancer incidence rates over time were consistently reported by Estonia.

Table 2. Sex-specific, Age-adjusted Breast Cancer Incidence Rates and Female-to-male Incidence Rate Ratios, All Ages, 1988–2002

Population (years)	Females			Males		
	Female Cases (n)	Incidence Rate (95% CI)	EAPC (95% CI)	Male Cases (n)	Incidence Rate (95% CI)	Female-to-Male Incidence Rate Ratio (95% CI)
<b>Asia</b>						
<i>India</i>	20,814	26.8 (26.4, 27.2)	0.63 (−0.47, 1.75)	321	0.42 (0.37, 0.47)	0.84 (−1.93, 3.69)
<i>Israel</i>	35,725	87.2 (86.3, 88.2)	<b>2.32 (1.13, 3.53)</b>	488	1.24 (1.13, 1.36)	0.35 (−6.59, 7.82)
<i>Japan</i>	37,846	30.4 (30.1, 30.7)	<b>2.35 (0.81, 3.92)</b>	221	0.18 (0.16, 0.21)	1.06 (−2.24, 4.47)
<i>Philippines</i>	13,171	54.2 (53.2, 55.1)	0.66 (−0.92, 2.26)	172	0.98 (0.83, 1.16)	2.10 (−2.81, 7.25)
<i>Singapore</i>	10,815	47.2 (46.3, 48.2)	<b>3.47 (3.18, 3.77)</b>	43	0.23 (0.17, 0.31)	−1.96 (−9.93, 6.73)
<i>Thailand</i>	2,078	18.0 (17.3, 18.8)	<b>4.17 (2.72, 5.63)</b>	17	0.16 (0.09, 0.26)	–
<b>Europe</b>						
<i>Austria</i>	5,168	68.9 (66.9, 70.9)	1.05 (−0.15, 2.26)	31	0.45 (0.30, 0.66)	12.04 (−0.16, 25.74)
<i>Denmark</i>	51,074	80.0 (79.2, 80.7)	<b>1.13 (0.56, 1.70)</b>	349	0.54 (0.48, 0.60)	0.59 (−1.70, 2.94)
<i>Estonia</i>	7,540	41.7 (40.7, 42.7)	<b>2.64 (1.32, 3.98)</b>	64	0.49 (0.37, 0.62)	1.02 (−0.06, 2.11)
<i>France</i>	51,487	83.6 (82.8, 84.3)	<b>1.59 (1.18, 2.01)</b>	455	0.77 (0.70, 0.85)	−0.32 (−3.76, 3.24)
<i>Iceland</i>	1,908	78.1 (74.5, 81.8)	0.91 (−3.10, 5.09)	23	0.93 (0.58, 1.42)	−1.74 (−20.66, 21.69)
<i>Italy</i>	54,097	77.6 (76.9, 78.3)	<b>2.61 (1.82, 3.41)</b>	560	0.83 (0.76, 0.91)	0.67 (−5.43, 7.16)
<i>Netherlands</i>	8,748	83.1 (81.3, 84.9)	<b>2.29 (0.92, 3.69)</b>	50	0.51 (0.38, 0.68)	0.45 (−5.15, 6.39)
<i>Poland</i>	15,681	50.9 (50.1, 51.7)	<b>2.06 (0.22, 3.94)</b>	122	0.50 (0.42, 0.60)	−2.28 (−5.67, 1.23)
<i>Slovakia</i>	23,474	42.5 (42.0, 43.1)	<b>2.19 (1.25, 3.15)</b>	220	0.48 (0.42, 0.55)	1.89 (−2.58, 6.57)
<i>Spain</i>	21,216	53.1 (52.3, 53.8)	<b>2.48 (1.52, 3.46)</b>	200	0.50 (0.43, 0.58)	3.85 (−0.95, 8.89)
<i>Switzerland</i>	8,307	75.7 (74.0, 77.5)	<b>2.15 (1.51, 2.79)</b>	55	0.55 (0.41, 0.73)	1.29 (−7.91, 11.41)
<i>UK</i>	212,665	76.4 (76.1, 76.8)	<b>1.27 (0.09, 2.47)</b>	1,373	0.50 (0.47, 0.53)	0.63 (−1.43, 2.72)
<b>America</b>						
<i>Brazil</i>	2,689	45.9 (44.2, 47.8)	<b>3.21 (1.90, 4.53)</b>	20	0.48 (0.29, 0.74)	<b>10.45 (2.09, 19.50)</b>
<i>Canada</i>	184,771	79.4 (79.0, 79.7)	0.32 (−0.43, 1.07)	1,307	0.59 (0.56, 0.62)	1.57 (−1.51, 4.75)
<i>Colombia</i>	4,538	40.5 (39.3, 41.8)	<b>2.54 (0.15, 4.99)</b>	20	0.23 (0.14, 0.35)	0.09 (−23.62, 31.16)
<i>Costa Rica</i>	6,296	32.0 (31.2, 32.8)	<b>3.25 (2.12, 4.39)</b>	54	0.30 (0.22, 0.39)	5.47 (−7.62, 20.41)
<i>Ecuador</i>	2,212	29.0 (27.8, 30.3)	0.87 (−0.96, 2.73)	19	0.29 (0.17, 0.46)	0.95 (−16.27, 21.72)
<i>USA</i>	241,875	90.7 (90.3, 91.0)	0.57 (−0.07, 1.22)	1,693	0.72 (0.69, 0.76)	0.30 (−2.10, 2.75)
<b>Oceania</b>						
<i>Australia</i>	114,877	78.1 (77.6, 78.6)	<b>2.11 (0.46, 3.79)</b>	804	0.55 (0.51, 0.59)	−3.38 (−5.94, −0.74)
						143.1 (133.5, 153.9)

Cancer Incidence in Five Continents: July 2011 Submission (1988–2002). Rates are per 100,000 woman/man years and age-adjusted to the World Standard Population. Italicized country names indicate data are regional or restricted by ethnicity. Abbreviations: CI, confidence interval; EAPC, estimated annual percentage change. “–” not able to be estimated due to one or more 3-year period having zero counts of cases. EAPCs in bold indicate statistical significance at alpha=0.05.





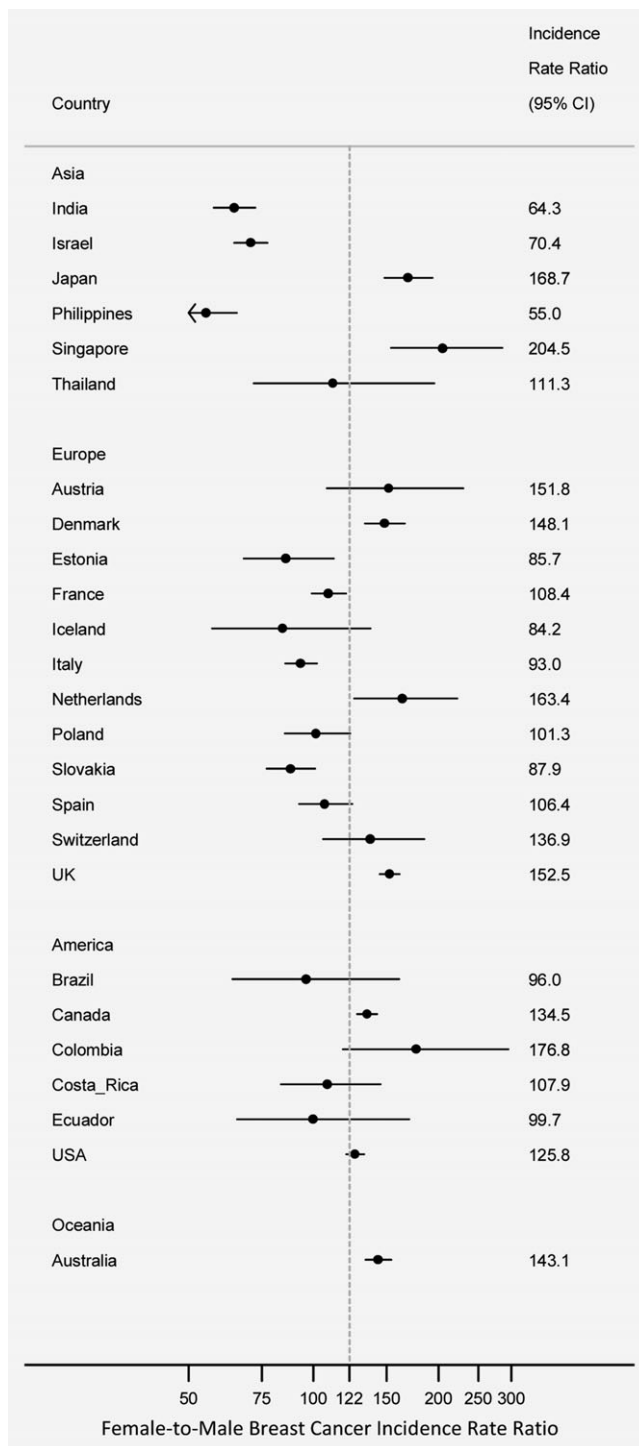
**Figure 1.** Trends in sex-specific, age-adjusted incidence rates for selected countries stratified by continent, all ages, 1958–2002. Rates are per 100,000 woman/man years and age-adjusted to the World Standard Population. Italicized country names indicate data are regional or restricted by ethnicity.

In Southern/Eastern Europe, Italy had the highest incidence of male breast cancer and female breast cancer. Male breast cancer incidence is markedly higher in North American countries compared with countries in South and Central America (except for Brazil in the most recent time period), and this observation is also true for female breast cancer. For countries that had the highest, and thus most stable, male breast cancer incidence rates, we plotted sex-specific incidence rates and female-to-male IRRs for individuals of all ages (Supporting Information Figure 1). For each of these countries, the female-to-male IRR over time represented a mirror image of male breast cancer incidence, indicating that this statistic is largely a function of the percentage change in male breast cancer incidence between each time period being large, relative to the percentage change in female breast cancer incidence rates.

A forest plot consisting of international female-to-male IRRs and corresponding 95% confidence intervals for the period 1988–2002 for individuals of all ages is shown in Figure 2. This graph illustrates how each country's IRR differs from each other as well as the same metric calculated for all countries combined (*i.e.*, a world estimate). As can be seen, there is a wide range of IRRs with in each continent, which reiterates the observation that IRR differences are not explained by continent. For many countries, the IRR estimates are significantly different from the world female-to-

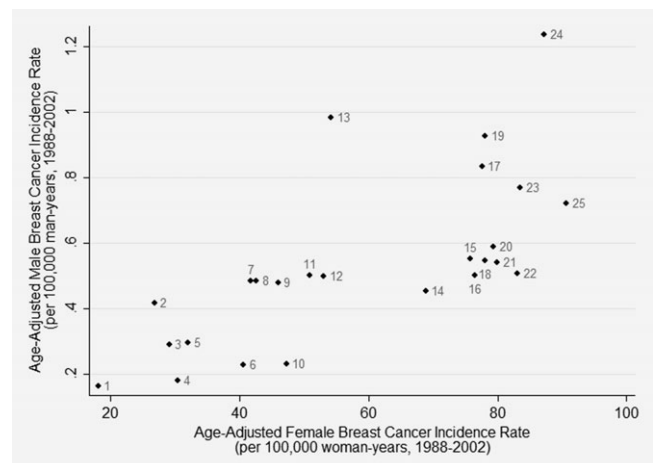
male IRR estimate for individuals of all ages, 1988–2002, of 122 (95% CI: 119–124), which is the result of large differences in both male and female breast cancer rates within and between country. World estimates of female and male breast cancer incidence rates, that contributed to this IRR, were 68.5 (95% CI: 68.3–68.6) per 100,000 woman-years and 0.56 (95% CI: 0.55–0.57) per 100,000 man-years, respectively.

We also stratified sex-specific, age-adjusted incidence rates by age group (<50 and ≥50 years) for the period 1988–2002 (Supporting Information Table 2). We found male breast cancer incidence was highest in Iceland in the <50 years age group and highest in Israel in the ≥50 years age group. These are distinct from the countries which have historically had the highest rates of female breast cancer—France in the <50 years age group and the United States in the ≥50 years age group. The lowest female and male incidence rates were generally observed in Thailand, regardless of age. Even though the rankings of countries for female and male breast cancer did not align perfectly, the Pearson correlation coefficient  $r$  for male and female breast cancer incidence rates during 1988–2002 for all ages was 0.69 (95% CI: 0.41–0.85;  $p < 0.0001$ ; Fig. 3). Differences in sex-specific IRRs (incidence rates for ages ≥50 years/incidence rates for ages <50 years) demonstrated that the impact of age on male breast cancer rates was greater, when comparing older to younger age



**Figure 2.** Forest plot of female-to-male breast cancer incidence rate ratios, all ages, 1988–2002. The gray-dashed line represents the female-to-male IRR of 122 for all countries combined. Abbreviation: CI: confidence interval.

groups, than that observed for female breast cancer. For example, in the United States, the male IRR was 31.6 compared with the female IRR of 11.0 (Supporting Information Table 2).



**Figure 3.** Correlation between age-adjusted male breast cancer incidence rate and female breast cancer incidence rate, all ages, 1988–2002. <sup>1</sup>Thailand, <sup>2</sup>India, <sup>3</sup>Ecuador, <sup>4</sup>Japan, <sup>5</sup>Costa Rica, <sup>6</sup>Colombia, <sup>7</sup>Estonia, <sup>8</sup>Slovakia, <sup>9</sup>Brazil, <sup>10</sup>Singapore, <sup>11</sup>Poland, <sup>12</sup>Spain, <sup>13</sup>Philippines, <sup>14</sup>Austria, <sup>15</sup>Switzerland, <sup>16</sup>United Kingdom, <sup>17</sup>Italy, <sup>18</sup>Australia, <sup>19</sup>Iceland, <sup>20</sup>Canada, <sup>21</sup>Denmark, <sup>22</sup>Netherlands, <sup>23</sup>France, <sup>24</sup>Israel and <sup>25</sup>United States.

Supporting Information Figure 2 portrays the relationships between sex-specific breast cancer incidence rates for individuals aged  $\geq 50$  years, 1998–2002, and health expenditure per capita for the year 2000. There was a positive association between age-adjusted female breast cancer incidence rates and health expenditure per capita ( $r = 0.68$ , 95% CI: 0.41–0.85;  $p < 0.0001$ ), with Japan a notable outlier. There was no significant relationship observed between age-adjusted male breast cancer incidence rates and health expenditures ( $r = 0.19$ , 95% CI:  $-0.23$  to  $0.54$ ;  $p = 0.37$ ). These correlations were similar when using individuals of all ages (data not shown). Lastly, assessment of incidence rates by health expenditure per capita indicated higher rates of female and male breast cancer, and higher female-to-male IRRs, for the second and third tertiles compared with the first tertile (Supporting Information Table 3).

An analysis of incidence rates from countries that introduced national screening programs for women shows that female breast cancer incidence rates increased by  $\sim 35\%$  from 60 to 81 per 100,000 women-years between the periods 1978–1982 and 1998–2002 (Supporting Information Table 4). Equivalent rates for the same time interval in Poland—a country that had not introduced a national screening program or widely utilized opportunistic screening during the period analyzed—increased 65% from 33 to 55 per 100,000 woman-years.

## Discussion

In this analysis of CI5 data, we have shown that male breast cancer rates are generally less than 1 per 100,000 man-years, in contrast to the much higher rates of female breast cancer, a fact underscored by the high female-to-male IRR of 122 for all countries combined. Although some of the EAPC's for

male breast cancer incidence during the period 1988–2002 were large, confidence in these estimates is wide due to the rarity of this disease. Conversely, female breast cancer incidence has been consistently increasing in a majority of countries assessed. Finally, the high correlation between male and female breast cancer incidences ( $r = 0.69$ , 95% CI: 0.41–0.85;  $p < 0.0001$ ) may indicate that some risk factors have common effects in both men and women.

Although this study has shown male breast cancer incidence rates to be universally low, relative to female breast cancer, there still existed dramatic and substantial variability between countries. The highest overall age-adjusted rates occurred in Israel (1.08 per 100,000 man-years), followed closely by the Philippines (0.99), Italy (0.80) and then France (0.75). The lowest rates of male breast cancer were recorded in Thailand (0.14), then Japan (0.17), Singapore (0.19) and Colombia (0.24). Part of the reason for such variability in rates may be population genetic susceptibility. For example, three founder mutations in *BRCA1* (185delAG and 5382insC) and *BRCA2* (6174delT) genes have been observed at higher frequency (>2% in total) in the Ashkenazi Jewish population than in the general US population.<sup>29,30</sup> A population bottleneck effect has been suggested to explain the increased frequencies of these haplotypes in the Ashkenazi Jewish population, as genetic drift and founder effects can quickly occur in small interbreeding populations, resulting in reduced genetic variation.<sup>31</sup> Previous studies have associated mutations in *BRCA1* and *BRCA2* with male breast cancer, which may explain the high male breast cancer incidence in Israel<sup>32</sup> and warrant further genetic studies in other populations with relatively high incidence rates. Although such studies should not be restricted to loci implicated in female breast cancer, the good correlation between male and female breast cancer incidence rates ( $r = 0.69$ ) may indicate that genetic susceptibility to this disease is similar in men and women. To utilize powerful agnostic approaches to determine whether male-specific genetic susceptibility breast cancer loci exist, it will be necessary to obtain a large numbers of cases—a difficult hurdle to overcome given the rarity of this malignancy in men.

The high correlation between female and male breast cancer incidence rates could indicate that environmental exposures which increase breast cancer risk are similar between men and women. Indeed, akin to female breast cancer, male breast cancer has been associated with conditions which imply a hormonal pathogenesis of disease including Klinefelter syndrome, obesity, physical inactivity and diabetes.<sup>14,15,17,33,34</sup> In addition, it has been suggested that male breast cancer may be etiologically comparable to late-onset female breast cancer, given similar prognostic characteristics, age-frequency distribution, and age-specific incidence patterns,<sup>35</sup> with sex steroid hormone-independent risk factors driving carcinogenesis.<sup>4</sup> These hypotheses deserve further attention. Conversely, within-country temporal trends for men and women have not always been equivalent and this may suggest sex-specific risk factors due to differences in ex-

posure or biological processing.<sup>36</sup> The most stark examples of sex-disparities in breast cancer incidence trends were observed in Japan (202% increase in female breast cancer rates, 10% decrease in male breast cancer rates), Israel (97% increase in female breast cancer rates, 19% increase in male rates), Austria (12% increase in female breast cancer rates, 113% increase in male rates) and India (20% increase in female breast cancer rates, 104% increase in male rates). Although a degree of caution is warranted in interpretation of such comparisons, given the relative instability of male rates, these observations are suggestive of different risk factor profiles for men and women. Indeed, major risk factors for female breast cancer stems from the varying reproductive and menstrual behavior of women which are obviously unique to this sex.<sup>3</sup> In addition, although there is evidence both for<sup>3,5,6</sup> and against<sup>7,8</sup> the thesis that male breast cancer patients have worse prognosis, cancer-specific survival, and overall survival, compared with female breast cancer cases, histopathologic evidence for differences in the frequency of breast cancer subtypes between men and women is strong and compelling.<sup>5,7,9,10</sup> Moreover, recent molecular analyses of male and female breast cancer have provided evidence for differences in the transcriptome<sup>11,12</sup> and cancer genome,<sup>13</sup> which may also support the idea of heterogeneity in pathogenesis of disease by sex.

Some of the perceived differences in breast cancer incidence trends between men and women could be an artificial effect created by the availability and/or use of screening modalities (e.g., self-examination, mammography).<sup>37–39</sup> There is evidence that high-income countries, such as the United States, may enhance diagnosis or even that some tumors may be the result of “overdiagnosis”<sup>40</sup>; that is, diagnosis of cancers that would never have caused symptoms or death. In support of these propositions, we found a strong correlation ( $r = 0.68$ , 95% CI: 0.41–0.85;  $p < 0.0001$ ) between female breast cancer incidence rates (for the period 1998–2002 and ages  $\geq 50$  years) and health-care expenditure per capita for the year 2000; Japan’s outlying status may be attributable to protective effects conferred by soy foods, which are rich in isoflavones.<sup>41</sup> For males, the correlation with health-care expenditure was much weaker ( $r = 0.19$ ), as may be expected given the absence of breast cancer screening programs for men. The finding that Polish female breast cancer incidence rates increased more than that of countries which introduced national screening programs, during the time period analyzed, could be interpreted as evidence against the idea of overdiagnosis, although such international comparisons could be complicated by differential use of self- and/or clinical breast examinations, differential underlying trends of incident disease, and differential ascertainment of disease. Within-country analyses are likely to better inform on the extent of overdiagnosis of breast cancer.<sup>40</sup>

Previous analyses of US SEER data have indicated that rates of male breast cancer have undergone a minor increase since the late 1970s.<sup>4,35,42,43</sup> Similar analyses have been conducted

for five European registries and Singapore,<sup>3</sup> and for the United Kingdom<sup>44</sup> but age-standardized incidence rates from these studies suggest that only Singapore has had a slight increase in male breast cancer incidence, with the rest of the countries appearing to have stable rates. In our analyses presented herein, which covers a much larger number of countries and periods of time than any previous study, we observed positive EAPCs for a majority of countries, with those from Austria (EAPC = 12.04), Brazil (10.45) and Costa Rica (5.47) of particular note. However, the rarity of this malignancy in men does not provide for high confidence in these estimates and a degree of caution is warranted in their interpretation.

There is evidence to suggest that between-country differences in female breast cancer incidence rates may be attributable to variability in exposure to breast cancer risk factors. For example, temporal trends demonstrate that female breast cancer incidence rates undergo gradual changes which would suggest changes in environmental exposures rather than a change in diagnostic procedures or introduction of a new screening test. In addition, studies have found that breast cancer risk is associated with country of residence rather than country of origin—Shin *et al.*<sup>45</sup> reported that breast cancer incidence among Asian-American women residing in the United States was 1.5–4 times higher than what was found in the women's own countries of origin. Moreover, the timing of ancestral migration has also been shown to affect this risk.<sup>46</sup> These effects of Western lifestyles and exposures may include reproductive factors, such as delayed childbearing, early age at menarche, or late age at menopause; a higher fat diet<sup>47</sup>; and/or use of hormonal replacement therapy for menopause.<sup>48</sup> Geographic differences in breast cancer incidence rates could be leveraged in the design of future migrant studies to aid determination of female, and possibly male, risk factors for this malignancy.

Strengths of this study include the use of Cancer Incidence in Five Continents data which has high data quality standards that have been applied across all volumes.<sup>18</sup> The use of female-to-male IRRs may also be viewed as a strength because this metric is less affected by changes over time in tumor definitions, coding assignments or diagnostic accuracy, relative to absolute differences in incidence rates<sup>49</sup>; however, female-to-male IRRs of breast cancer should be interpreted with caution as they are still vulnerable to effects of sex-related differences in early detection practices, health care utilization, illness behavior, and physician behavior,<sup>50</sup> and the effect of such may be exacerbated given the rarity of this tumor in men. Female-to-male IRRs are also limited by their dimensionless scale, thus we also present sex-specific incidence rates to enable comparisons of absolute differences. Lastly, varying calendar periods of cancer registry coverage reduced parts of our analysis to the shorter period of 1988–2002, to enable a fair comparison of statistics presented.

In this analysis of 8,681 male breast cancer cases and 1.14 million female breast cancer cases, we have shown that male breast cancer rates are generally less than 1 per 100,000 man-years, in contrast to the much higher rates of female breast cancer, a fact underscored by the high female-to-male IRR of 122 for all countries combined. In addition, this study has shown that female breast cancer incidence has been increasing over time for a majority of countries assessed, while male breast cancer incidence trends are more variable, with only a minority of countries presenting evidence for an increase. Variability in the female-to-male IRR may reflect enhanced diagnosis, and potentially overdiagnosis, in females and/or sex differences in exposures and pathogenesis. Conversely, the high correlation between male and female breast cancer incidences may indicate that both sexes share common risk factors for this disease.

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