On the avoidability of breast cancer in industrialized societies: older mean age at first birth as an indicator of excess breast cancer risk

Isabelle Soerjomataram · Eero Pukkala · Hermann Brenner · Jan Willem W. Coebergh

Abstract *Background* Breast cancer incidence continuous to increase. We examined at population level the association between the relative excess risk of breast cancer and previous age of mother at first birth. *Method* Incidence of breast cancer in 34 industrialized countries was obtained from the GLOBOCAN 2002 and SEER databases. Data on age of mother at first birth was collected through national statistics offices. National relative excess risk (RER) was calculated by subtracting the lowest age-specific incidence rate from the rate in each population, and dividing the difference by the latter. *Results* The national RER in 2002 correlated closely with a higher average age at first birth in 1972, 1982, 1992 and also 2002, Pearson correlation [r] being 0.83, 0.79, 0.72 and 0.61, respectively; $P < 0.0001$. RER of breast cancer in 2002 for those aged 15–44 years correlated closely with the mean age at first birth in 1982 and 1992 (r: 0.81 and 0.75; $P < 0.0001$), whereas RER for those aged 45–54 years correlated strongly with age at first birth in 1972 and 1982 (r: 0.81 and 0.76; $P < 0.0001$), and for those aged 55–64 years with age at first birth in 1972 (r: 0.77; $P < 0.0001$). *Conclusions* The rising age at first childbirth of mothers has been followed by marked increases in breast cancer incidence. Later age at first birth seems to characterize secular diffusion of 'modern' lifestyles with a potentially large impact on increased breast cancer risk, and hence should be accompanied by greater opportunities for prevention through modifiable risk factors.

Introduction

Global trends in breast cancer incidence have been attributed to various factors including reproductive history and hormonal factors, female body composition and nutritional factors, also alcohol consumption [1–3]. Higher socioeconomic status has also been associated with a higher risk of breast cancer [4]. Furthermore, increased use of mammography has increased the detection rate leading to a higher observed breast cancer incidence [5]. Reproductive-related factors including age at birth of first child and number of children has been suggested as one of the major determinants of breast cancer incidence [2], and has been attributed to 28% of its incidence [6]. Women who had their first birth at age 35 or older exhibit a 60% higher risk of breast cancer than women who had their first child at age 20–21 [7]. There are large differences between countries in the age of the mother at first birth [8], as well as in the incidence of breast cancer [9]. Recent and historical data on national fertility patterns are available and comparable for most western populations. However the role of

I. Soerjomataram (✉) · J. W. W. Coebergh
Department of Public Health, Erasmus MC, P.O. Box 2040, 3000
CA Rotterdam, The Netherlands
e-mail: i.soerjomataram@erasmusmc.nl

I. Soerjomataram · J. W. W. Coebergh
Comprehensive Cancer Centre South, P.O. Box 231, 5600 AE
Eindhoven, The Netherlands

E. Pukkala
Institute for Statistical and Epidemiological Cancer Research,
Finnish Cancer Registry, Helsinki, Finland

H. Brenner
Division of Clinical Epidemiology and Aging Research, German
Cancer Research Center, Heidelberg, Germany

mother's age at first birth in the past, marking current breast cancer risk has not yet been examined. Thus, we assessed the association between age at first birth and the excess risk of breast cancer a few decades later using data from 34 industrialized countries.

Methods

Materials

We performed this study within the framework of the European collaborative project Eurocadet, which estimates the future potential of cancer prevention based on recent trend in cancer incidence and its related risk factors [10]. Incidence data was obtained from GLOBOCAN 2002 [11] and the SEER database for white non-Hispanic Americans [12]. We included European countries (Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Former Yugoslavic Republic of Macedonia, The Netherlands, Norway, Poland, Portugal, Romania, Serbia and Montenegro, Slovakia, Slovenia, Spain, Sweden, Switzerland and United Kingdom) as well as Australia, Canada, Israel, New Zealand and the USA. In GLOBOCAN 2002 incidence rates were estimated based on the best available data from national or regional cancer registries. Methods of estimation and correction for suspected under-recording have been described elsewhere [11]. We included only countries with more than 1 million inhabitants. Data on mother's average age at first birth in 1972, 1982, 1992 and 2002 or approximately the same period were retrieved from EUROSTAT [8] or National Statistics Institutes for non-European countries (Table 1). In the United States, we only included data of non-Hispanic whites.

Statistical analysis

Incidence rates for breast cancer were calculated by 5-year age groups and age-adjusted (world standard population) for truncated age categories (15–44, 45–54, 55–64 and 65+). Excess incidence was calculated by subtracting the lowest rate age-specific observed in the selected countries from the respective national rate. Incidence rate was lowest in Czech Republic for age group 15–44, in Lithuania for age groups 45–54 and 65+, and in Latvia for age group 55–64. Absolute numbers of excess cases were calculated by multiplying the excess incidence rates by the size of the population of the country of interest in the same period and age group [13]. Relative excess risk (RER) was calculated

as the ratio of excess incidence and observed incidence in a country. We used the Pearson correlation coefficient to quantify the relationship between national RER and current as well as past average age of the mother at first birth. We also examined the correlation of age at first childbirth in 1972 and 1982, and 1992 with RER for those aged 45–54 and 15–44 years, respectively. We assumed that most women of 45–54 years in 2002 had their first childbirth between the 1970s and the 1980s. The age group 15–44 years mostly comprised breast cancer cases older than 35 years, who typically had their first childbirth in between the 1980s and the 1990s. In addition, we correlated RER for those aged 55–64 years in 2002 to average age at first child in 1972. These women most likely had their first child between 1965 and 1975. Correlation analysis was performed only with the year 1972, because data of the 60s were scarce. In order to take the large variation of population sizes of the included countries into account, correlation coefficients were weighted by population sizes in the respective age groups.

Results

The highest overall age-adjusted relative excess risk of breast cancer was found for Belgium, France, New Zealand and the Netherlands (59%, 57%, 55% and 54%), whereas the lowest was in Romania and Czech Republic (9% and 14%) (Table 1). Incidence rates for two age groups (45–54 and 65+ years) were lowest in Lithuania, which explains the low RER for this population (1%). In countries with the highest RER in 2002, the average age at first birth was 24–25 years in 1972, 25–26 years in 1982, 27–28 years in 1992 and 28–29 years in 2002. In contrast, mothers in countries with the lowest RER in 2002 had their first child at 23 years in 1972, 22–24 years both in 1982 and 1992 and 24–26 years in 2002 (Table 1). Figure 1 illustrates the correlations between RER in 2002 for 15–44 years, 45–54 years and 55–64 years with mean age at first child in 1972, 1982 and 1992. Mean age at first childbirth in 1982 and 1992 correlated closely with RER of breast cancer in 2002 for those aged 15 to 44 years (r: 0.81 and 0.75; P-value < 0.0001). Among 45 to 54 year old breast cancer cases, the corresponding correlations were 0.81 for 1972, and 0.76 for 1982. The correlation for average age at birth of first child in 1972 and RER for those aged 55 to 64 in 2002 was 0.77 (P-value < 0.0001). Finally, we found a decreasing magnitude of the correlation between RER in 2002 for 15+ years with increasing calendar year of mean age at first child (figure not shown); Pearson correlation coefficients (r) were 0.83 for 1972, 0.79 for 1982, 0.72 for 1992 and 0.61 for 2002 (P-value < 0.0001).

Table 1 Fertility pattern and relative excess risk of breast cancer by period

Countries	Average age at first birth (years)				Relative excess risk in 2002 (%)			
	1972	1982	1992	2002	All ages	Age group 15–44	Age group 45–54	Age group 55–64
Australia [a]	n.a.	25.5	28.0	30.2	49.9	46.9	50.4	59.5
Austria	n.a.	24.1 [c]	25.0	27.4	45.9	47.0	36.7	48.9
Belgium	24.3	24.9	26.7	27.6 [i]	59.1	59.8	58.9	59.3
Bulgaria	22.1	21.9	21.9	23.9	21.1	25.2	11.7	18.3
Canada	n.a.	24.9	26.0	27.7	48.0	43.7	47.8	57.5
Croatia	n.a.	23.5 [d]	24.7 [g]	25.9	37.5	37.1	34.7	40.5
Czech Republic	22.6	22.4	22.5	25.6	14.0	ref	27.6	37.4
Denmark	24.0	25.0	26.9	28.5 [j]	48.8	43.2	51.3	63.0
Estonia	23.9	23.3	22.8	24.6	19.4	19.2	21.5	17.8
Finland	24.6	25.4	26.7	27.6	48.2	42.7	59.6	56.6
France	24.3	25.3	27.4	27.9 [k]	57.4	56.7	58.8	61.2
Germany	24.1	25.4	26.9	28.6	49.6	47.7	50.2	54.5
Greece	n.a.	24.2	26.0	27.9	22.0	19.1	27.4	21.6
Hungary	22.7	22.6	23.3	25.6	29.3	21.9	36.2	41.6
Ireland	25.8	25.6	26.7	28.0	41.5	35.6	49.9	54.7
Italy	24.9	25.3	27.3	28.6 [l]	50.0	51.5	47.2	45.2
Israel	n.a.	n.a.	24.4 [h]	25.8	46.5	38.1	55.5	62.9
Latvia	n.a.	22.9	22.8	24.9	16.6	20.6	8.7	ref
Lithuania	n.a.	24.2	23.1	24.3	0.9	1.4	ref	0.1
Macedonia	n.a.	na	23.5	24.7	26.7	27.4	22.5	24.9
New Zealand	n.a.	25.6	28.4	30.4	55.3	53.7	52.2	66.4
Norway	n.a.	24.8 [e]	25.9	27.2	40.8	34.5	48.3	53.7
Poland	23.0	23.4	23.4	25.0	17.5	12.0	30.4	22.7
Portugal	n.a.	24.0	25.2	26.8	33.3	35.5	35.1	26.2
Romania	22.5	22.5	22.6	24.1	9.2	5.4	18.5	14.2
Serbia and Montenegro	n.a.	23.5 [f]	24.2	25.5	37.0	39.6	37.0	30.5
Slovakia	22.7	22.7	22.6	24.7	17.1	15.1	18.2	13.7
Slovenia	23.3	23.1	24.1	27.2	30.5	27.4	30.6	33.7
Spain	22.5	25.4	27.5	29.2	25.1	25.4	28.4	23.3
Sweden	26.0	25.6	26.7	28.3	47.6	41.3	51.8	64.6
Switzerland	25.4	26.5	27.8	29.0	51.1	50.4	44.3	57.4
The Netherlands	24.8	26.0	28.0	28.7	54.5	53.3	57.1	53.2
United Kingdom	24.1	25.4	27.8	29.3	52.7	50.1	54.2	58.5
United States [b]	n.a.	n.a.	25.1	26.1	52.9	48.1	51.3	64.6

n.a.: not available; ref: reference group; [a]median age at first birth within marriage; [b]data was not categorized by non-Hispanic white and Hispanic white before 1989; [c]data in 1984; [d]1983; [e]median age at first birth within marriage in 1976–1980; [f]data in 1983; [g]data in 1993; [h]data in 1994; [i]data in 1997; [j]data in 2001; [k]data in 2000; [l]data in 1998

Discussion

We observed a strong correlation between the overall excess incidence of breast cancer in 2002 and the average age of the mother at first birth in 1972–2002. Both current and past average age at first childbirth were related with recent excess risk of breast cancer. The earliest period of exposure assessment correlated best with the current excess risk of breast cancer. For those aged about 40 at breast cancer diagnosis in 2002, mean age at first childbirth in 1982 and 1992 correlated closely with their excess risk. For those aged about 50 years at diagnosis, age at first birth in 1972 and in 1982 correlated with their current excess risk. Finally, for those aged about 60 years at diagnosis, age at first birth in 1972 strongly correlated with their current excess risk.

We determined excess breast cancer incidence as the difference between national incidence rates and the lowest
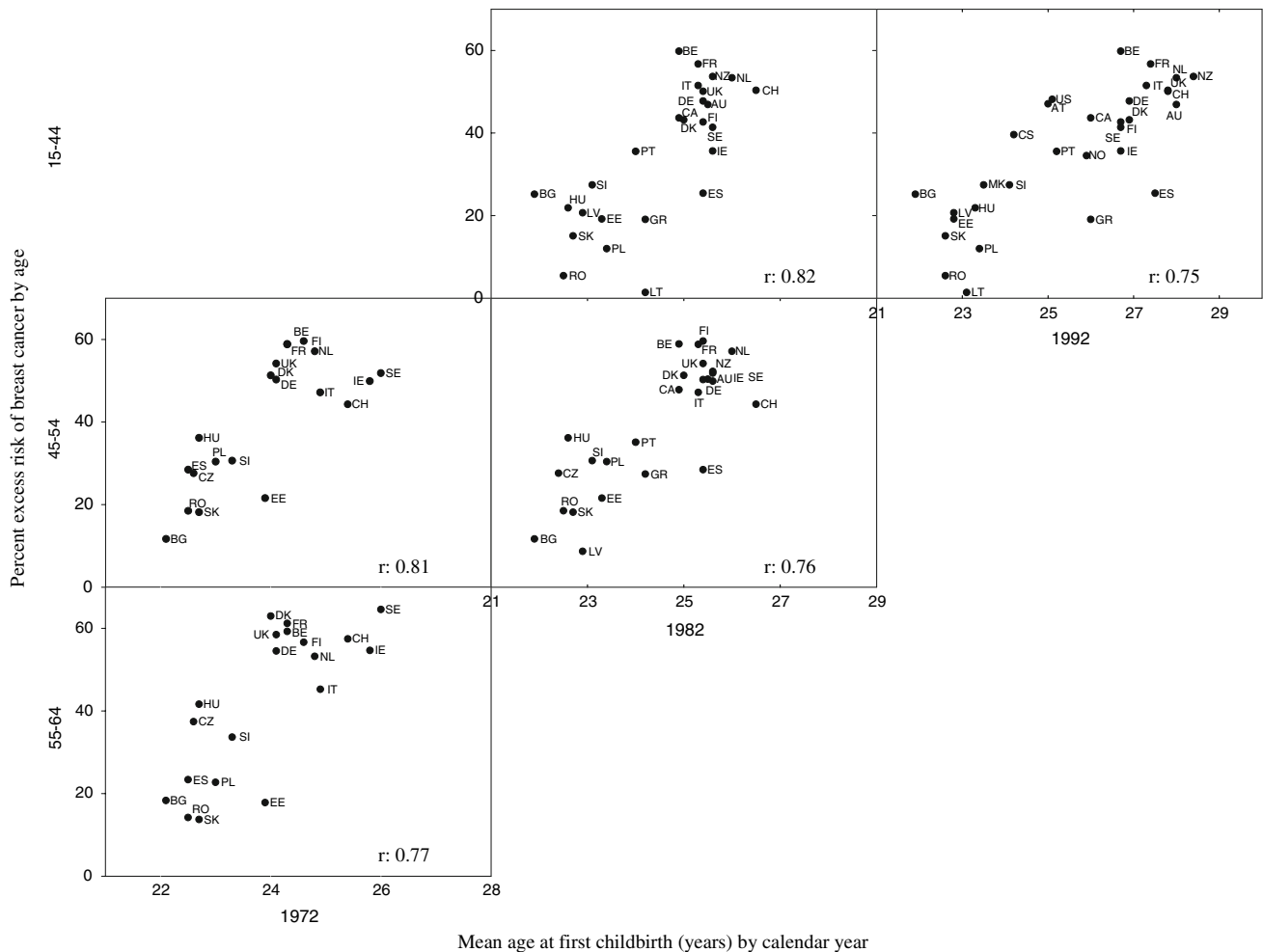
Fig. 1 Plot of mother's average age at first birth and the percent excess risk of breast cancer among women in 2002, by age groups and calendar years AU: Australia, AT: Austria, BE: Belgium, BG: Bulgaria, HR: Croatia, CA: Canada, CZ: Czech Republic, DK: Denmark, EE: Estonia, FI: Finland, FR: France, DE: Germany, GR: Greece, HU: Hungary, IE: Ireland, IT: Italy, LV: Latvia, LT: Lithuania, MK: Macedonia, NZ: New Zealand, NO: Norway, PL: Poland, PT: Portugal, RO: Romania, CS: Serbia and Montenegro, SK: Slovakia, SL: Slovenia, ES: Spain, SE: Sweden, CH: Switzerland, NL: The Netherlands, UK: United Kingdom and US: United States of America

observed rate. Hence, the relative excess in 2002 is supposed to be largely due to variations in external risk factors across populations, such as age at birth of first child, and hardly to genetic differences [13]. Though the latter may have played a interactive role, the prevalence of predisposing breast cancer genes is too low to explain these interpopulation differences [14]. Our results are consistent with previous studies [15–17] and supported by biological evidence of the role of pregnancy in the pathogenesis of breast cancer [18].

In affluent countries, the higher excess risk of breast cancer may be caused by practices of early detection and screening programs, especially among women over 50 [5]. In such populations, age at first birth also tends to be higher. However, increasing breast cancer rates have also been observed in countries without national screening

programs (e.g. Czech republic, Slovenia, Slovakia, Estonia and Norway) [5]. Moreover, in countries where organized screening is present such as in the Netherlands and in Finland, increasing rates of breast cancer have been observed before the screening period [5]. Thus, it is unlikely that higher breast cancer rates in industrialized societies are entirely attributable to screening.

The excess of cases of breast cancer in 2002 reflects past exposure to multiple risk factors. Availability of comparable data on other risk factors is limited for most countries, and we were therefore unable to adjust for possible confounders, such as parity or duration of hormonal contraception use, which are also related to breast cancer risk [19]. Moreover as with any correlation study, observed correlations may be due to these other factors [20]. However, studies have shown that after correcting for other

breast cancer risk factors such as oral contraceptive use and number of children, age at first birth remained an independent indicator of higher breast cancer risk among women who were older at birth of their first child [17, 19].

We correlated average age of mother at first birth to breast cancer risk, hence our finding might not sufficiently apply to the increasing proportion of childless women with an even higher breast cancer risk [21]. The proportion of women still childless at age 40 might therefore be an indicator for the proportion of nulliparous and be used in the analysis to adjust for it. However historical data for this indicator is limited and when available (e.g. in 2002), [22] we found a very high correlation with average age at first birth (r: 0.90, data not shown). The observed correlation in this study thus partly reflects the risk of childless women; nations in which women were older at delivery of their first child also comprise a higher proportion of childless women and a higher excess breast cancer risk.

We found the largest increase in age at first birth in countries with the highest relative risk of breast cancer between 1982 and 2002, being 3–4 years in the UK, the Netherlands, France Spain and Australia. By contrast, average age at first birth in countries like Bulgaria, Slovakia, Lithuania, Latvia and Poland hardly changed between 1982 and 1992, but increased by an average of 2 years between 1992 and 2002. Overall, the trend in postponing children seems to be continuing [22]. Despite some flattening in the Netherlands, postponement of childbearing is likely to be resumed, and mean age at first birth is predicted to increase up to 33 years [23]. A further increase of breast cancer incidence might be the result.

We observed a marked relationship between average age at first birth in 1972, 1982, and 1992 and excess risk among women diagnosed in 2002 with breast cancer aged 55–64, 45–54 and 15–44. Most women diagnosed with breast cancer at age 45 to 54 in 2002 probably had their first child 20–30 years before 2002, thus mostly around 1980. For age groups 15–44 and 55–64 years, year of first childbirth was mostly around 1990 and 1970, respectively. The correlation between RER in 2002 and age at first delivery is thus equally seen among pre-menopausal and post-menopausal breast cancer [16]. Furthermore, we observed the correlation to decrease with shorter time since exposure (age at first birth): the correlation between RER in 2002 for all age groups (15+) and mean age at first birth in 1972 was 0.83, continuously decreasing to 0.61 in 2002. Findings were similar across all age groups, suggesting a lag time of 20–30 years until variation in age at first birth is projected on the risk of breast cancer in the population.

What about the association between age at first birth in 1992 and 2002 and excess breast cancer risk in 2002? Most women who gave birth to their first child in 1992 or 2002 were too young to account for the association with breast cancer risk in 2002. However, risk factors for breast cancer are generally clustered more in countries with a high incidence of breast cancer [16]. For example; younger age at menarche (by 1.1 year) has been reported in countries with a high breast cancer risk, such as United States and Wales as opposed to Taiwan and Japan with a lower risk [16]. Similarly, lower parity and higher prevalence of nulliparity was observed in high breast cancer risk countries [16]. Furthermore, in countries with a higher risk of breast cancer higher body mass index was also observed, [16] possibly also reflecting the combination of a diet high in calories and lack of exercise. Finally, wider use of alcohol among women [24] and post-menopausal hormonal therapy [25, 26] are generally observed in more affluent regions, thus also in populations with a higher incidence of breast cancer. To summarize, older age at first child delivery probably is also a risk indicator of clustering of risk factors in western populations. This implies that a part of excess cases might be preventable by other means.

Basically, opportunities appear to be small of modifying some of the known risk factors for breast cancer, especially the timing of conceiving children. Delayed childbirth represents increasing educational opportunities and career choices for most women [22]. As a consequence, enhancing the potential for altering modifiable risk factors becomes even more important: minimizing alcohol intake [27], avoiding weight gain by the combination of a balanced diet and enough physical activity [28] and promoting breast-feeding [29] should, to a certain extent, reduce the risk of breast cancer. Finally, this study suggests age at first birth as a useful indicator for forecasting future incidence of breast cancer.

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