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HRT and breast cancer: Impact on population risk and incidence

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Abstract

This study has calculated the potential impact of hormone replacement therapy (HRT) on breast cancer incidence in Australia and has estimated how changes in prescribing HRT to women could affect this risk. The effects of HRT on breast cancer incidence was estimated using the attributable fraction technique with prevalence data derived from the 2001 Australian Health Survey and published rates of breast cancer relative risks from HRT use. In Australia, 12% of adult women were current HRT users and in 2001, 11 783 breast cancers were reported. Of these, 1066 (9%) were potentially attributable to HRT. Restricting HRT use to women aged less than 65 years, ceasing HRT prescribing after 10 years or limiting combined oestrogen and progesterone HRT to five years (but otherwise keeping prescription levels to 2001 levels) may reduce the annual breast cancer caseload by 280 (2.4%), 555 (4.7%) or 674 (5.7%), respectively. In conclusion, this study has demonstrated that when HRT prevalence is relatively high, the effect on breast cancer incidence in the population will be significant. A small modification in HRT prescribing practices may impact breast cancer incidence in Australia with associated financial and health care provision implications.

Keywords: Breast cancer; Hormone replacement therapy; Oestrogen; Progesterone

1. Introduction

The incidence of breast cancer within a population is influenced by a combination of effects including the underlying incidence, the effect of population screening and socioeconomic effects that may influence women's decisions to commence families. Whilst a woman's baseline inherited risk will not change, fertility, diet and medication may modify subsequent risk. Hormone replacement therapy (HRT) has been identified as a risk factor for breast cancer development. Recent large studies and randomised controlled trials have demonstrated that both type and duration of HRT use affect a women's risk of developing breast cancer [1–9]. Media publicity has increased awareness of the potential risks of breast cancer with HRT and some have reported a reduction in HRT prevalence since the publication of high profile trials [10]. Current estimates suggest that prescriptions for oral HRT have fallen by 38% to 1993 levels [21] and, therefore, that the impact of HRT on breast cancer incidence may be reducing.

We have previously shown that for an individual, the additional risk of developing breast cancer from oestrogen-only HRT or short-term (~5 years) use of combined HRT containing oestrogen and progesterone is small [22]. For example, a 50-year old woman has a 6.1% risk of developing breast cancer in the subsequent 30 years of her life. Five years of oestrogen-only or combined HRT will impart an additional risk of only 0.2% or 0.5%, respectively. However, at the national or state level, the effect of HRT on breast cancer incidence may

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be more significant with frequent use of HRT in a population.

The idea that a small risk for the individual can be magnified into a significant population effect is not new [11] and has been described for other disease processes such as heart and lung disease. Strategies to control the burden of a disease in a population may be more profitably focused on the large proportion of the population at a small or moderate risk rather than a few individuals at high risk. We have applied this concept to HRT and breast cancer to determine the relative effects on annual breast cancer incidence in women with short-term, low-risk HRT use and in the relatively few women on prolonged, high-risk HRT.

This study has aimed to quantify the population effect of HRT on breast cancer incidence in Australia and estimate the number of cancers that may be attributable to HRT in populations with different HRT prevalence. We discuss that a woman's breast cancer risk and quality of life with HRT could be balanced by the cost and the potentially increased burden of the disease in the community.

2. Patients and methods

2.1. Data collection

The prevalence of HRT use was estimated from the latest (2001) quinquennial Australian Health Survey. This national study involved 50 000 people and contained an additional Women's Supplementary Health Form administered to 9750 women over the age of 18 years that questioned *inter alia* their HRT status and duration of HRT use. Approximately 10% of the women in each age group did not respond to the HRT question in the 2001 census and were excluded from subsequent calculations. The data were extrapolated to provide estimates of proportion and duration of HRT use for the entire Australian population by 5-year age group and this allowed an estimation of age-specific HRT prevalence. For each age group, the duration of HRT use was subdivided according to the number of years of treatment (<1 year, 1–5 years, 5–10 years, 10 or more years) and the Australian Health Survey provided weighted estimates of numbers for the Australian population. Where some subdivisions contained small numbers, age groupings were condensed to <45 years, 5-yearly age groups to 65 years, and 65+ years.

Breast cancer incidence data were retrieved from the Australian Institute of Health and Welfare website (www.aihw.gov.au). The reported incidence could have been elevated by the increased detection of breast cancers by the national screening programs. Mammographic screening was introduced in Australia in 1991 but uptake was not widespread until 1999 when 57.1% of 50–69 year-old women attended screening. These rates were adjusted to counter the screening effect [12,13] estimating the "underlying" incidence of breast cancer from age, period, cohort model based on the 1972–2001 data using the average stable period effect 1972–1989. The annual incidence of breast cancer in Australia is approximately 11 800 new cases per year, of which over 9650 are diagnosed in women aged 40–79 years (Australian Institute of Health and Welfare). Information about the relative risks for breast cancer with HRT use was obtained from the UK Million Women Study [5].

2.2. Data analysis

The attributable factor (AF) is the proportion of the disease that is due to a particular factor and depends on the prevalence and relative risk (RR) of that risk factor in the population. The AF for HRT in breast cancer for each age group was calculated by the indirect method [14] using the specific prevalence and the relative proportions of use according to HRT formulation. These were taken from the Australian Health Survey data and studies of HRT use [15,16] and the relative risk of the breast cancer by age and duration of HRT use (from Beral and colleagues [5]). Thus, for each age group a series of AFs specific to HRT type and duration of use could be calculated. Summation of these AFs provides the age specific AF that can be applied to a population. The indirect method of estimation or AF is [14]:

$$\mathrm{AF} = \frac{p(\mathrm{RR}-1)}{p(\mathrm{RR}-1)+1},$$

where

p = HRT prevalence

× proportion of use by HRT medication type.

Application of the age-specific AF to the breast cancer incidence (I_{pop}) using the direct method [14] allowed calculation of the age-specific "underlying" incidence of breast cancer in the population who have never been exposed to HRT (I_{never}) and the incidence attributable to HRT (I_{HRT}).

$$\mathrm{AF} = \frac{I_{\mathrm{pop}} - I_{\mathrm{never}}}{I_{\mathrm{pop}}}$$

And thus

$$I_{\mathrm{never}} = I_{\mathrm{pop}}\left[1 - \left(\frac{p(\mathrm{RR}-1)}{p(\mathrm{RR}-1)+1}\right)\right]$$

and

$$I_{\mathrm{HRT}} = I_{\mathrm{pop}} - I_{\mathrm{never}}.$$

Multiplication of these incidence values to the number of females in the population (taken from the Australian

2001 census) allowed the calculation of the numbers of breast cancers within each age group and the cases attributable to different HRT formulations. The number of cases attributable to HRT for each age group in Australia was calculated in a similar way from the published numbers of reported breast cancers (www.aihw.gov.au).

Using different values of HRT use by formulation, prevalence and duration, with the above formulae, new AFs for a hypothetical population was calculated. Application of these AFs to the breast cancer incidence (I_{never}) allowed the new population breast cancer incidence to be estimated and calculation of potential changes in breast cancer caseload if prescribing patterns changed. Four scenarios were applied to the existing prescribing patterns for 2001:

1. HRT prevalence in the population reduced to two-thirds of 2001 levels in women of all ages. This is the estimate of HRT use in Australia in 2003 [21].
2. HRT prevalence maintained at 2001 values for women under 65 years and no HRT use in women age 65 years or older.
3. HRT use maintained at 2001 estimates but no oestrogen-only HRT or combined HRT taken beyond 10 years duration.
4. HRT prescribing levels maintained at 2001 levels but the duration of combined HRT use is limited to five years.

3. Results

In 2001, based on the Australian Health Survey, 11.8% of women were current users of HRT with a peak prevalence of 37.7% in 55–59 year olds (Table 1). Over one-quarter of Australian women between 50 and 70 years were current users of HRT (Fig. 1).

The duration of HRT use varied according to the age group questioned. For women aged 50 years or less, most had taken HRT for less than 5 years (Table 1) but over two-thirds of women aged 55–65 years, had used HRT for at least five years. Prolonged HRT use, over 10 years duration, was most frequently observed for women over 55 years and more than one-half of current HRT users aged 60 years or older had been taking HRT for more than 10 years.

The proportion of breast cancers attributable to differing categories of HRT use is demonstrated in Table 2. For women aged 40–55 years, a total of 3723 breast cancers were reported in Australia, of which 286 (7.7%) may be attributable to HRT use. The burden of HRT attributable breast cancer in this age group was due to short term (<5 years) HRT use, accounting for 144 (3.9%) breast cancer cases. For women aged 60–64 years HRT could be implicated in 217 of 1366 (15.9%) reported breast cancers and

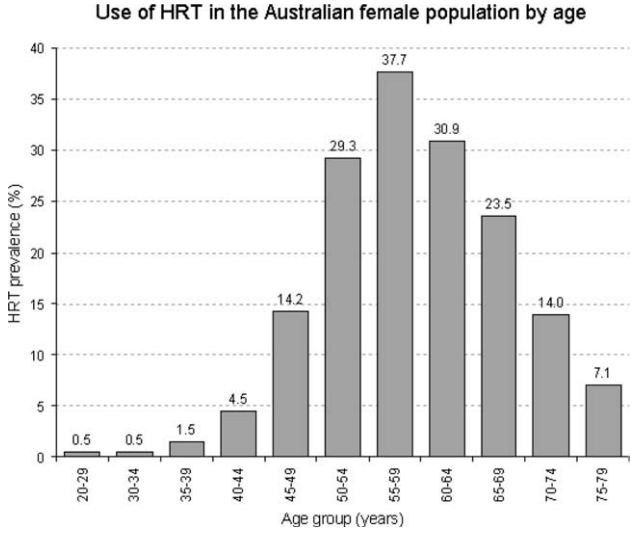

Fig. 1. Use of HRT in the Australian female population by age.

Table 1
Hormone replacement therapy use in Australian women in 2001

Age group (years)	No HRT* use	Current HRT users				HRT prevalence (%)
		Duration of HRT use				
		<1 yr	1 < 5 yrs	5 < 10 yrs	⩾10 yrs	
	'000[a]	'000[a]	'000[a]	'000[a]	'000[a]	
20–44	3200.2	13.7	20.4	4.5	6.7	1.4
45–49	531.2	26.9	38.9	13.9	7.9	14.2
50–54	412.7	23.7	84.6	36.4	26.4	29.3
55–59	272.8	8.3	40.2	55.3	61.1	37.7
60–64	255.2	4.3	19.0	29.7	61.1	30.9
65+	691.6	3.3	20.8	28.5	80.1	16.1
All	5363.7	80.2	223.9	168.3	243.3	11.8

HRT*, hormone replacement therapy

Source. Australian Health Survey – 2001, Women's Supplementary Questionnaire.

[a] Thousands, numbers in the data fields are to be multiplied by 1000.

Table 2
Proportion of breast cancers in each age group attributable to HRT* according to formulation and duration of use

Age group (years)	Duration of E + P HRT[a]				Duration of E-only HRT[b]				All HRT use (%)
	<1 yr (%)	1 < 5 yrs (%)	5 < 10 yrs (%)	⩾10 yrs (%)	<1 yr (%)	1 < 5 yrs (%)	5 < 10 yrs (%)	⩾10 yrs (%)	
40–44	0.2	0.7	0.2	0.4	−0.1	0.2	0.1	0.1	1.9
45–49	0.8	1.8	1.0	0.6	−0.3	0.6	0.3	0.2	5.0
50–54	0.7	4.2	2.9	2.4	−0.3	1.5	0.8	0.7	12.9
55–59	0.3	2.6	5.3	6.5	−0.1	0.9	1.5	2.0	19.0
60–64	0.2	1.4	3.4	7.3	−0.1	0.5	1.0	2.2	15.9
65–69	0.1	1.1	2.3	6.8	0	0.4	0.6	2.1	13.3
70–74	0.1	0.8	1.5	4.6	0	0.3	0.4	1.3	8.9
75–79	0.0	0.3	0.8	2.2	0	0.1	0.2	0.7	4.3

HRT*, hormone replacement therapy.
[a] E + P HRT, combined oestrogen and progesterone HRT.
[b] E-only HRT, oestrogen only HRT.

Table 3
Calculated breast cancer incidence in Australian women according to age and HRT use

Age group (years)	Breast cancer incidence (cases/100 000)					
	Reported rate[a]	Screening effect rate[b]	Underlying rate I_{pop}[c]	HRT user rate I_{HRT}		HRT non-user rate I_{never}
				E + P	E only	
40–44	115.2	12.2	103.0	0.6	0.1	102.3
45–49	188.4	36.1	152.3	8.2	1.5	142.6
50–54	250.7	44.0	206.7	25.6	6.6	174.5
55–59	302.4	67.0	235.4	44.7	12.8	177.9
60–64	337.2	84.1	253.1	41.5	12.1	199.5
65–69	324.0	64.9	259.1	23.3	6.7	229.1
70–74	329.7	40.2	289.5	26.0	7.5	256.0
75–79	309.7	54.2	255.6	22.9	6.6	226.1

HRT, hormone replacement therapy. I_{HRT}, breast cancer incidence attributable to HRT. I_{never}, breast cancer incidence in non-HRT users. E + P, oestrogen and progesterone HRT.
E only, oestrogen only HRT.
[a] *Source*. Australian Institute of Health and Welfare – 2001.
[b] Rate estimated using stable period effect from Taylor and colleagues [15].
[c] I_{pop}, underlying population breast cancer incidence adjusted for screening effect.

prolonged (⩾10 years) HRT use may be responsible for 130 (9.5%) cases.

Application of these attributable fractions to the underlying breast cancer incidence allowed the breast cancer incidence in non-users of HRT, oestrogen-only HRT and combined HRT users to be calculated. The effect of HRT on breast cancer incidence and caseload is most marked for the age groups where HRT use is highest. For example, in the age cohort 55–59, 57.5 (12.8 oestrogen-only HRT and 44.7 combined HRT) of the 302.4 cases per 100 000 female population (19.0%) could be attributed to HRT use (Table 3). Fig. 2 illustrates the cases of breast cancer in the population by age group and those potentially attributable to different HRT formulations.

In 2001, there were 11 783 cases of breast cancer and potentially 1066 (9.0%) were attributable to HRT. This effect was most marked in women aged 50–64 years. Table 4 shows how policy changes for HRT prescribing

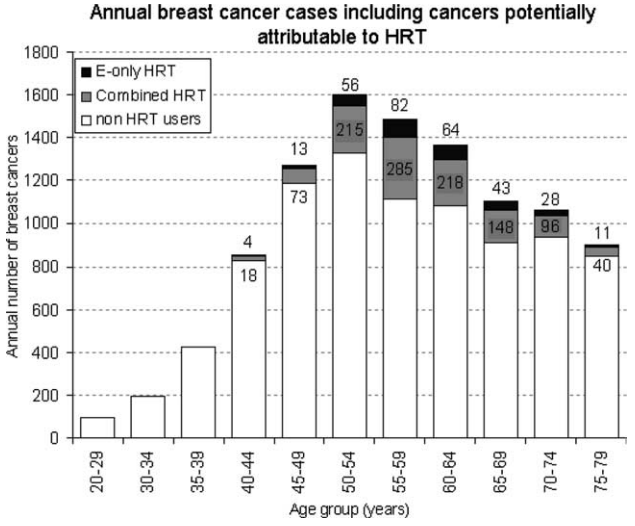

Fig. 2. Annual breast cancer cases including cancers potentially attributable to HRT.

Table 4
Number and proportion (%) of breast cancers potentially attributable to HRT use in Australia

Age group (years)	Reported breast cancer cases[b], *n*	Number and proportion (%) of annual breast cancers potentially attributable to HRT[a]				
		HRT use 2001 levels	HRT use at projected 2003 levels[c]	HRT use limited to women age >65 years	E-only HRT and E + P HRT limited to 10 years	E + P HRT use limited to five years
			Scenario 1	Scenario 2	Scenario 3	Scenario 4
40–44	852	(1.9)	(1.2)	(1.9)	(1.4)	(1.2)
45–49	1269	(5.0)	(3.4)	(5.1)	(4.3)	(3.4)
50–54	1602	(12.9)	(8.1)	(12.9)	(9.4)	(7.1)
55–59	1484	(19.0)	(11.5)	(19.0)	(9.2)	(5.9)
60–64	1366	(15.9)	(9.8)	(15.9)	(5.4)	(4.4)
65–69	1103	(13.3)	(8.4)	(0)	(4.0)	(3.7)
70–74	1066	(8.9)	(5.7)	(0)	(2.7)	(2.6)
75–79	900	(4.3)	(2.9)	(0)	(1.4)	(1.3)
Women (all ages)						
Projected annual breast cancer cases		11783	11392	11503	11228	11109
Breast cancers potentially attributable to HRT (%)		1066 (9.0)	675 (5.9)	786 (6.8)	511 (4.6)	392 (3.5)

E + P HRT, combined oestrogen and progesterone HRT.
E-only HRT, oestrogen only HRT.
[a] Calculated as the proportion of breast cancers potentially attributable to HRT for each 5-year age group in women aged 40–79 years.
[b] *Source*. State and Territory Cancer Council Registries.
[c] Projected HRT use in 2003 is approximately two-thirds of 2001 levels [21].

could modify the numbers of breast cancers in Australia. Current estimates of HRT use suggest that, in Australia, HRT prevalence has fallen by one-third since 2001. With this scenario, the annual number of breast cancers could fall to 11 392 of which 675 (5.9%) may be due to HRT. If combination HRT prescribing was limited to a maximum of five years, the annual breast cancer caseload could fall to 11 109 of which 392 (3.5%) may be attributable to HRT.

4. Discussion

This study describes a methodology that allows estimation of the numbers and proportions of additional breast cancers from HRT for any country from the prevalence of HRT, breast cancer incidence, and female population data. Reducing the prevalence or duration of HRT may reduce the annual incidence of breast cancer cases.

This paper uses established statistical methods that have been described elsewhere for smoking and lung cancer and family history and breast cancer [12,17,18]. The breast cancer relative risk data used to estimate the attributable fractions were derived from the Million Women Study, a UK cohort study on HRT and breast cancer incidence. This study assessed over one-quarter of the United Kingdom female population aged 50–65 years where approximately 70% of women attended the screening program [5]. The risks used should be relevant to an Australian population as HRT prevalence and proportions of HRT use by formulation are very similar between the countries [15,16,19]. We have adjusted for the effect of breast screening on the reported breast cancer incidence, correcting for the detection of prevalent cases during the widespread introduction of a national screening program in Australia between 1991 and 1999. Participation by women in Australia is now similar to reported attendance rates in the UK screening program.

There are some potential weaknesses in our methodology. Although there has been some criticism that the UK study may overstate the breast cancer risk with HRT [20], we have applied the quoted relative risks as there are small standard errors and the study provides values for breast cancer risk with differing durations of use. This information allows calculation of the changes in cancer workload for hypothetical populations.

The Supplementary Women's Health Questionnaire provided information about HRT use in Australia, in 2001. This large survey questioned 9750 women in all States and Territories and provides HRT information for the entire Australian population. It may be more accurate and applicable than other published Australian HRT prevalence studies that only provide data relevant to one State [15,16]. The number of non-responders was only 10% in each age group and these were excluded from the calculations. However, since the publication of studies claiming adverse effects from prolonged HRT use, the prevalence of HRT use in Australia has dropped [9,10]. Our data suggests that current

prescribing for oral HRT has fallen by 38% to 1993 levels [21] and, therefore, the number of breast cancers attributable to HRT may now be lower.

The breast cancers detected for women taking HRT may be due to the accelerated hormonal stimulation of impalpable, pre-malignant lesions within a woman's breast. Malignant transformation may normally take several years to develop in these areas but this transition may have been accelerated by HRT. Thus, the calculated relative risk attributed to HRT could be explained by "borrowing" potential breast cancers from the future, generating a perceived increase in breast cancer risk with HRT use.

However, the strengths of our study are that it uses established methods to calculate the burden of breast cancer in Australia. This information would be of use in the planning of health care provision and the methodology and formulae may be used in any population where the breast cancer incidence and HRT prevalence are known. This would allow other nations to estimate the impact of HRT on the annual breast cancer burden. Changing the values of HRT prevalence allows theoretical estimates of changes in breast cancer incidence to be calculated. Indeed, we estimate that use of HRT in Australian women has fallen by one-third since 2001 (Table 4, Scenario 1) and thus the numbers of breast cancers potentially attributable to HRT will reduce from 1066 to 675 per annum.

The techniques described here would be applicable to other disease processes and risk factors and could be used to identify population subgroups that may contribute more significantly to the burden of that disease in the community. This would allow healthcare agencies to target accurately these specific groups to reduce the incidence of a disease more effectively. For example in Australia, the numbers of cancers that may be due to HRT vary among different age groups of the population due to the variations in patterns of HRT use. In women aged 40–55 years the majority of HRT attributable breast cancers are due to short-term (<5 years) HRT use (Fig. 2), despite the lower breast cancer relative risks of 1.74 and 1.25 for combined HRT and oestrogen-only HRT, respectively, for five years duration of HRT use [5]. This is because the majority of HRT users have been taking HRT for less than five years. Conversely, in women aged 60–64 years prolonged (~10 years) use of HRT has a larger impact on the population breast cancer incidence than short-term (<5 years) use (Fig. 2). This can be explained by the combination of the larger proportion of older women using HRT for greater than 10 years with the higher breast cancer relative risks generated by prolonged HRT use.

A woman's cumulative absolute breast cancer risk to age 79 years will fall with advancing years because although the age-specific breast cancer incidence increases with age there remain fewer years exposed to that risk [12]. We have shown previously that HRT will generate a small additional risk of breast cancer in an individual [22] and the benefit in lifestyle and reduction in perimenopausal symptoms may be considered sufficient to warrant this extra risk. However, this view needs to be balanced because a very small increase in risk at an individual level will be magnified to produce a noticeable change in population cancer caseload where HRT use is high.

This paper presents important data relevant to Australian public health medicine and demonstrates that although using HRT may generate a small additional risk of breast cancer for an individual, when the prevalence of HRT in the community is high, the effect on breast cancer incidence in the population will be more pronounced. A small modification to HRT prescription practices, for example, by restricting its duration of use or limiting HRT to women of a certain age, may impact breast cancer caseload in Australia. This has important implications for health care funding and service provision.

Conflict of interest statement

None declared.

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