

Could Recent Decreases in Breast Cancer Incidence Really Be Due to Lower HRT Use? Trends in Attributable Risk for Modifiable Breast Cancer Risk Factors in Canadian Women

C. Ineke Neutel, PhD, FACE, FISPE,¹ Howard Morrison, PhD²

ABSTRACT

Objectives: Recent downward trends in breast cancer incidence have been attributed to declining use of hormone replacement therapy (HRT). To determine whether this is a credible conclusion, this study calculated population attributable risk (PAR) for HRT and other modifiable breast cancer risk factors.

Methods: PAR calculation needs both the prevalence of a risk factor, and the relative risk (RR) for breast cancer incidence for that risk factor. Prevalences were calculated for Canadian women, aged 50-69, participating in the National Population Health Survey, 1994-2006. RR were derived from published research: 1.4 for HRT use, 1.4 for excessive alcohol use, 1.15 for physical inactivity, 1.25 for smoking, 1.4 for BMI over 30 kg/m². Trends for PAR were calculated for the risk factors separately, as well as combined. Age-adjusted breast cancer incidence rates were calculated for Canadian women aged 50-69 for the years 1994-2004.

Results: Between 1998 and 2004, PAR for HRT decreased by 50%. PAR for other risk factors showed only small changes, and the combined PAR decreased by 18.6%. Age-adjusted breast cancer incidence for women aged 50-69 peaked in 2000 at 330.0/100,000, then dropped by 17.2% by 2004.

Conclusion: Patterns of PAR for HRT use in Canada are consistent with the noticeable decrease in breast cancer incidence observed for women of the same age group. Combining PAR for all risk factors indicated that changes in HRT use overpowered any trends of other risk factors. The combined PAR suggest that alterations in lifestyle could have considerable impact on breast cancer incidence.

Key words: Breast cancer incidence; population attributable risk; hormone replacement therapy; alcohol; physical activity; obesity

La traduction du résumé se trouve à la fin de l'article.

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Many menopausal women have unpleasant symptoms which can be alleviated by hormone replacement therapy (HRT).¹⁻³ For decades, the putative protective effects against heart disease and osteoporosis were also considered incentives for HRT use.^{4,5} When results from the Women's Health Initiative (WHI) and the Heart and Estrogen/progestin Replacement Study (HERS) provided no evidence for heart disease protection – in fact, even suggesting an increased risk⁶⁻⁸ – dramatic decreases in HRT use ensued.⁹⁻¹¹

HRT use is also known to increase the risk of breast cancer. In many countries, breast cancer incidence appears to be on a downward trend in recent years. In Canada, age-adjusted incidence rates for breast cancer changed from a high of 105.1/100,000 in 1999 to a low of 96/100,000 after 2002.¹² Similar decreases were seen for other countries.^{9,13,14} Because of HRT's known breast cancer risk, researchers were quick to attribute such declines in breast cancer rates to lower HRT use.^{15,16} Not all agreed.^{17,18}

However, it is not clear whether a roughly 4% drop in overall breast cancer incidence is a drop of reasonable magnitude to be attributable to the observed decrease in HRT use. Population attributable risk (PAR) can be used to estimate the proportion of breast cancer incidence attributable to risk factors such as HRT. Accordingly, the objective of this study is to estimate trends in breast cancer PAR due to five modifiable breast cancer risk factors: HRT use, excessive alcohol consumption, obesity, lack of physical activity and smoking. Smoking is not as generally accepted as a breast can-

cer risk factor, but a recent Canadian expert panel concluded that there is a small, but real, increase.¹⁹

In order to estimate the PAR, risk measures for each of the risk factors are needed. Increases in breast cancer risk for HRT use varies with type of HRT used. For overall HRT use, breast cancer risk increased about 50%.^{15,16,20} For women taking the estrogen and progestin (E&P) combination, breast cancer risk doubled.^{15,16} The increased risk for unopposed estrogen varied from a high of an 80% increase to no effect at all.^{16,21,22} Finding risk estimates for the other risk factors in populations comparable to postmenopausal Canadian women was not easy and only the most relevant studies will be mentioned here. Increased breast cancer risk related to alcohol use varied largely with how alcohol was measured, e.g., a 30% increase for 'current consumption,' 70% for 'heavy drinking' (two or more drinks per day), or 40% for lifetime consumption of one drink daily.^{23,24} Smoking led to an increased risk of 30-40% among long-term smokers.^{25,26} A recent expert panel suggested an increased risk of 25% for current smokers as a summary measure of the increased risk.¹⁹ For body weight, an increase of 47% breast cancer risk was found for women who gained 30 or more pounds after age 18.²²

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Table 1. Age and Modifiable Breast Cancer Risk Factors of Canadian Women, Aged 50-69, Weighted Percentages

Risk Factors	N=	Years Interviewed						
		1994	1996	1998	2000	2002	2004	2006
		wt%*	wt%	wt%	wt%	wt%	wt%	wt%
Age (years)	50-59	58.3	56.9	55.9	54.8	56.1	57.9	58.5
	60-69	41.7	43.1	44.1	45.3	43.9	42.1	41.5
HRT use	yes	24.0	30.2	34.2	32.4	29.8	15.3	13.7
Smoking	yes	15.7	17.0	17.1	15.6	14.8	13.7	12.8
Inactive	yes	60.8	61.7	54.9	57.6	49.9	51.0	45.6
Obese	>30 kg/m ²	16.3	16.4	20.7	20.6	21.9	22.7	24.1
Alcohol	9+/wk	4.4	4.4	5.3	4.6	5.0	5.1	6.6
Mammograms	last 2 yrs	59.7	63.6	69.5	75.0	75.8	74.5	73.2

* wt% means weighted percentage.

Physical activity was found to have a protective effect, with an increased risk for inactive women of 25% in one study and 15% in another.^{27,28}

METHODS

The National Population Health Survey (NPHS) started with a random sample of 17,276 Canadians selected in 1994 and reinterviewed biannually. For this study, data for all women between ages 50 and 69 in the years 1994-2006 were included. To keep the age composition constant, women who reached 70 between interviews were dropped and women reaching age 50 were added. Data for this cohort were statistically weighted in order to be representative of all Canadian women of this age range.

Information used included age, HRT use, smoking, physical activity, body mass index (BMI), and alcohol use. The HRT question was "In the past month, did you take hormones for menopause or aging symptoms?" A three-part physical activity index was dichotomized as the least active category versus the other two combined. Drinking nine or more drinks in the previous week was considered excessive alcohol use. Body mass index (BMI) was calculated as weight divided by height², and a BMI of 30 kg/m² or more was considered obese.

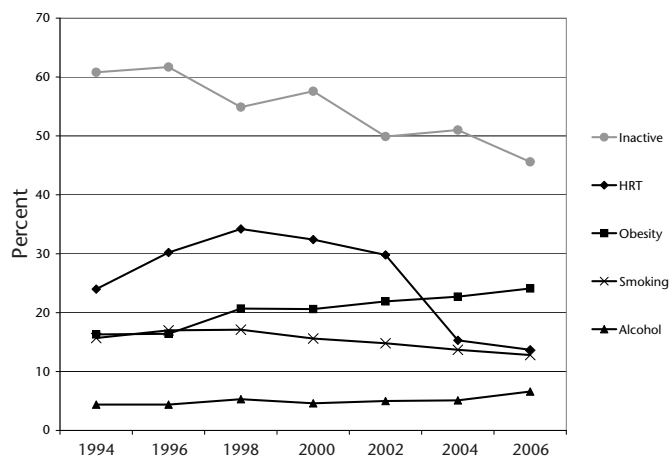
PAR was calculated as a percentage, using the formula $(r-1)/(1+p(r-1))$ multiplied by 100.²⁹⁻³¹ Prevalences of the risk factors, 'p,' were weighted percentages of the risk factors in this study population, 1994-2006. Increased breast cancer risks 'r' used for the calculations were: 1.4 for HRT use, 1.4 for alcohol consumption more than nine drinks per week, 1.15 for physical inactivity, 1.25 for current smokers, 1.4 for obesity, based on published literature.^{22,27,29} For the combined PAR, the formula: $PAR(\text{combined}) = 1 - (1-PAR_1) * (1-PAR_2) * (1-PAR_3) * (1-PAR_4) * (1-PAR_5)$ was used.

RESULTS

The study population varied from 1,078 to 1,450 over the years (Table 1). Changes in size of study population resulted from women turning 50 entering, and women turning 70 dropping out. Obesity and excessive alcohol drinking showed small but steady increases over the years, while smoking and lack of physical activity showed small but steady declines (Table 1 and Figure 1). HRT use showed a unique pattern in that the use increased until 1998, then gradually decreased until 2002, followed by a sudden drop to half its previous value. Although mammograms are not a modifiable risk factor like the others, the rates of use were included in the table because of its known ability to modulate breast cancer incidence.

Age-standardized breast cancer incidence rates for women ages 50-69 showed a steady increase until 2000 followed by a downturn

Figure 1. Trends in modifiable breast cancer risk factors in Canadian women aged 50-69, weighted for the Canadian population



(Figure 2). From 2000 to 2004, the age-adjusted breast cancer incidence rates decreased by 19.7%.

Table 2 and Figure 3 present the PAR for risk of breast cancer incidence for the five modifiable risk factors. The risk factor prevalence 'p' was taken from the weighted percentages of Table 1 and the 'r' as listed in the Methods section. The PAR for HRT users increased from 8.8% in 1994 to 12% in 1998, then dropped by 51.7% by 2004. The percent drop was calculated as a percentage of the 1998 HRT use. The combined PAR increased to 29.5% in 1998, then dropped by 18.6% by 2004. The PAR for obesity increased over the years of the study while PAR for physical inactivity decreased. PAR for smoking and alcohol remained relatively level.

DISCUSSION

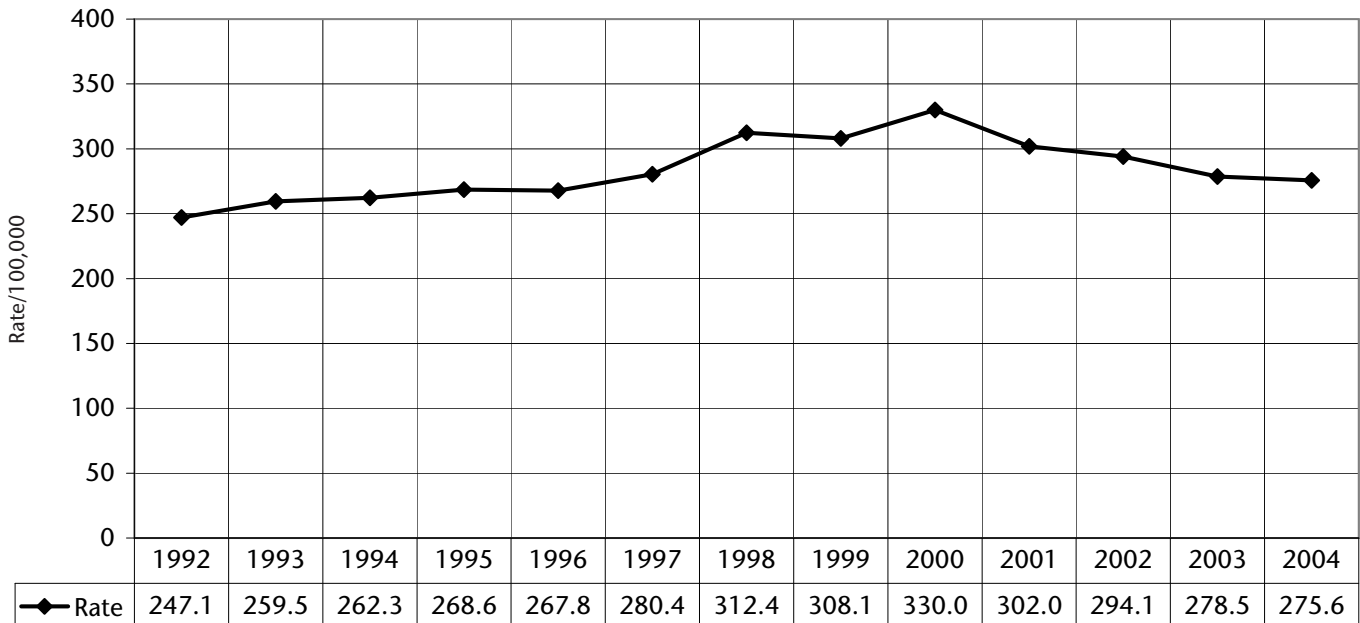
Our findings indicated a rise and fall in HRT use since 1994, accompanied by a similar rise and fall in age-adjusted breast cancer incidence for women of the same age group, but with the peak two years later. Both the temporal relation and the pattern of rise and fall in the PAR for HRT and breast cancer incidence are consistent with a possible causal association between the two. The other risk factors for which PAR were calculated showed smaller changes, but the combined PAR decreased by 18.6% between 1998 and 2004 with the 'r,' as used, following the pattern of changes in the HRT use. Overall, it may be concluded that the patterns and size of changes in HRT use are consistent with those of declines in breast cancer incidence. In terms of the question, "Could decreases in breast cancer incidence really be due to lower HRT use?", the answer is yes, the magnitude of the decrease in HRT use could

Table 2. Canada: PAR Due to Modifiable Breast Cancer Risk Factors, Weighted to be Representative of Canadian Women, Aged 50-69

Modifiable Risk Factors		PAR* as Percentage						
		1994	1996	1998	2000	2002	2004	2006
1.	HRT (r=1.4)	8.8	10.8	12.0	11.5	10.7	5.8	5.2
2.	Obese (r=1.4)	6.1	6.2	7.6	7.6	8.1	8.3	8.8
3.	Alcohol (r=1.4)	1.7	1.7	2.1	1.8	2.0	2.0	2.6
4.	Smoking (r=1.25)	3.8	4.1	4.1	3.8	3.6	3.3	3.1
5.	Physical inactivity (r=1.15)	8.4	8.5	7.6	8.0	7.0	7.1	6.4
Combined PAR†		25.8	27.8	29.5	28.9	27.7	24.0	23.6

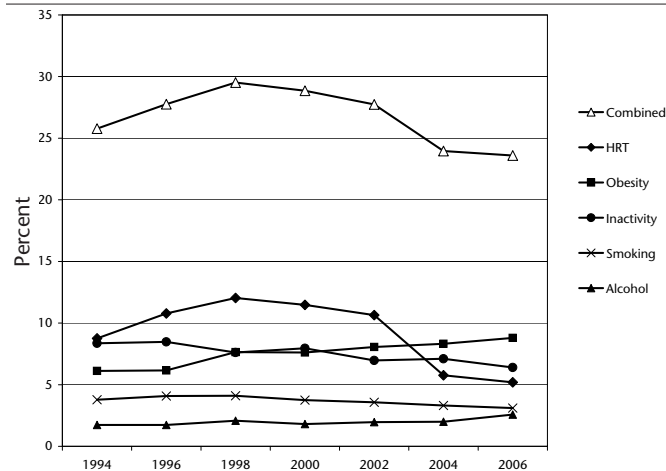
* $PAR = p(r-1)/(1+p(r-1))$
 † Combined $PAR = 1 - (1-PAR_1) * (1-PAR_2) * (1-PAR_3) * (1-PAR_4) * (1-PAR_5)$

Figure 2. Age-standardized breast cancer incidence/100,000, Canadian women, 50-69



Data source: Public Health Agency of Canada, Chronic Diseases Prevention and Control. The standard population used was that of Canadian women of this age group for the year 2000.

Figure 3. Trends in population attributable risk (PAR) for modifiable breast cancer risk factors, ages 50-69



account for the observed decrease in breast cancer incidence. While this is not the same as proving causality, it does remove a potential obstacle in the way of proving same.

Another such obstacle might be that the time lag of two years between the decrease in HRT use and the decrease in cancer incidence does not seem long enough. However, Colditz points out that HRT likely acts as a promoter rather than an initiator and a short time span is consistent with the action of a promoter.³² One

may wonder whether this means that the breast cancer is only delayed for a while, since, presumably, the initiator is still present, and another promoter may come along to continue the process where the HRT stopped. In this case, a resurgence of breast cancer incidence may occur in the near future.

As with every other data set, these data have both strengths and limitations. Strengths include the large number of variables available for seven biannual interviews on each respondent. These seven interviews ranged over a crucial time period when major changes in HRT use took place. Data limitations include the self-reported data, although other research found that this was not an important issue for HRT use.³³ Another limitation is the absence of useful information such as menopausal status or estrogen receptor status. A concern is the need to use overall HRT use rather than E&P use which has the highest breast cancer risk.^{15,16} Since risk measurements based on E&P use were less reliable and since E&P prevalence was not available for all NPHS cycles, and less accurate when available, it was decided to use the overall HRT risk and prevalence instead.

A variable that could affect breast cancer incidence trends is the use of mammograms. When a mammogram program is started, breast incidence goes up because more new cases are detected. If later the mammogram program is pursued less ardently, the incidence will go down. Mammograms in Canadian women increased steadily up to about 75% in the time period 2000-2004. This pat-

tern does not show the changes needed to explain a decrease of breast cancer incidence after 1998.

Two variables were needed to complete the formula for PAR, the first of which was 'p', the prevalence of the potential risk factor. The prevalences of modifiable breast cancer risk factors were derived from a statistical sample of the Canadian population and thus are a very good estimate. HRT prevalence in Canada increased during most of the 1990s, followed by a slow decrease, then a plunge to half its prevalence. Other risk factors showing decreasing trends were physical inactivity and smoking while obesity and excessive alcohol use showed increasing trends. The increases in obesity and in physical activity seem rather at odds. One may have some doubt about the actual increase in physical activity. Much of the physical activity index for the NPHS is based on self-reported sports and leisure activities and the answers may be somewhat optimistic; they may also not take into account decreasing activities of everyday life.

The other variable needed to estimate the PAR was 'r', the size of the risk. The selection of 'r' based on published studies was difficult and imprecise, especially for risk factors other than HRT. Risks measured varied substantially from study to study, likely because of differences in the source populations, such as age distribution, ethnic composition, definitions of variables measured. The choices of RR used were based on the results of the most relevant data available. Some decisions were rather subjective aiming for intermediate values, since no more rigorous approach was possible. Unfortunately, changes in the 'r' made noticeable differences in PAR. This does not negate the value of these results. The PAR calculated provide a reasonable, albeit not precise, estimate. Furthermore, changes in 'r' might change the level of PAR but do not change the patterns and trends of PAR, and conclusions regarding trends can be considered valid.

Even with the less than perfect 'r' for calculating the PAR, it is clear that changes in the prevalences of these modifiable cancer risk factors have the potential of a considerable impact on breast cancer incidence in Canada. With the 'r' used in this study, one quarter of new cases of breast cancer could theoretically be prevented. It is also clear that the recent decreases in HRT use are quite capable of considerable reductions in breast cancer rates, and that the decreases in breast cancer seen so far may in fact have resulted from same. Furthermore, the PAR calculations indicate that changes in lifestyle can be quite influential in breast cancer risk and the potential for further decreases in breast cancer incidence is sizable.

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RÉSUMÉ

Objectifs : Les tendances à la baisse récemment observées dans l'incidence du cancer du sein ont été attribuées à la diminution de l'usage du traitement hormonal substitutif (THS). Pour déterminer la crédibilité d'une telle conclusion, la présente étude a calculé la fraction étiologique du risque (FER) pour le THS et d'autres facteurs de risque modifiables du cancer du sein.

Méthode : La FER combine la prévalence d'un facteur de risque dans la population avec le risque relatif de l'incidence du cancer du sein associée à ce facteur de risque. Les prévalences ont été calculées chez les Canadiennes de 50 à 69 ans ayant participé à l'Enquête nationale sur la santé de la population (1994-2006). Les risques relatifs ont été tirés des résultats de recherche publiés : 1,4 pour l'utilisation du THS; 1,4 pour la consommation excessive d'alcool; 1,15 pour l'inactivité physique; 1,25 pour l'usage du tabac et 1,4 pour un IMC supérieur à 30 kg/m². Les tendances de la FER ont été calculées pour les facteurs de risque pris séparément d'abord, puis combinés. Les taux d'incidence du cancer du sein normalisés selon l'âge ont été calculés pour les Canadiennes de 50 à 69 ans, de 1994 à 2004.

Résultats : De 1998 à 2004, la FER du THS a diminué de 50 %. Les FER des autres facteurs de risque pris séparément présentaient de légères variations, alors que la FER de tous les facteurs de risque combinés a diminué de 18,6 %. L'incidence du cancer du sein normalisée selon l'âge chez les femmes de 50 à 69 ans a culminé en 2000, avec un taux de 330,0/100 000; en 2004, ce taux avait diminué de 17,2 %.

Conclusion : Les tendances de la FER du THS au Canada correspondent à la diminution considérable de l'incidence du cancer du sein observée chez les femmes du même groupe d'âge. La FER des facteurs de risque combinés indiquait que des changements apportés au THS surpassaient toute tendance des autres facteurs de risque. Ce résultat laisse également croire qu'une modification des habitudes de vie pourrait avoir des répercussions importantes sur l'incidence du cancer du sein.

Mots clés : incidence du cancer du sein; fraction étiologique du risque; traitement hormonal de substitution; alcool; activité physique; obésité



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