Hormone replacement therapy and the risk of breast cancer in postmenopausal women

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
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The association between the use of hormone replacement therapy (HRT) and postmenopausal breast cancer was examined in the Ontario component of the Enhanced Cancer Surveillance (ECS) Project. Cases comprised 404 postmenopausal women ages 35-74 with incident, pathology confirmed breast cancer. They were compared to 403 postmenopausal controls, frequency matched to the cases on age strata. Information on risk factors was obtained through self-administered questionnaires. Women who used HRT for a duration of ten or more years (long-term users), within the past 5 years, were at an increased risk of breast cancer, relative to non-users (OR=2.00, 95% CI=1.13-3.53). The odds ratio for long-term users of progesterone in combination with estrogen was non-significantly higher (OR=4.03, 95% CI=1.11-14.64) than that for long-term users of estrogen alone (OR=1.76, 95% CI=0.94-3.30). Odds ratios were not significantly modified by family history, age group, smoking status, body mass index, alcohol consumption, type of menopause or ovarian status.
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Chapter 1
Introduction

1.1 Rationale

As the production of estrogen by the ovaries declines, millions of women at menopause face the dilemma of whether or not to compensate by taking estrogen in hormone replacement therapy (HRT). They want the health benefits of estrogen among which are a reduced risk of heart disease (Stampfer & Colditz, 1991; Stampfer et al., 1991), osteoporosis (Weiss et al., 1980), Alzheimer’s disease (Waring et al., 1999) and possibly colon cancer (Grodstein et al., 1999) as well as diminished menopausal symptoms such as hot flashes, night sweats and vaginal dryness (Hunt & Vessey, 1987), but the fear of an increased risk of breast cancer holds many women back.

Epidemiologic evidence suggests that the association between HRT and breast cancer is plausible. Breast tissue is estrogen dependent and responds to the hormone’s growth-stimulating effects (Mauvais-Jarvis et al., 1986). Estrogen has been shown to play a critical role in the promotion of breast cancer (LaCroix & Burke, 1997). It has already been established that endogenous estrogens influence breast cancer risk; late onset of menopause, early age at menarche and older age at first full-term pregnancy all increase a woman’s risk of developing breast cancer (Bernstein & Ross, 1993). Reasoning by analogy, these data implicate exogenous estrogens as well, in the etiology of breast cancer.

The effect of HRT use on the risk of breast cancer remains a contentious issue, in spite of the many studies examining the association. There seems to be agreement that ever use is not associated with an increased risk (Steinberg et al., 1991; Colditz et al., 1993b). Studies have
mixed results for long-term use (Colditz et al., 1993b; Yang et al., 1992; Kaufman et al., 1991). Many of the studies do not reflect the current protocol for HRT use. There is a particular lack of data addressing risk by type of HRT; some women now take concomitant progestin for protection against endometrial cancer, which is associated with use of estrogen alone. In addition, HRT was formerly advocated principally for short-term use to alleviate the immediate symptoms of estrogen deficiency. Now that it is an elective treatment, advocated as prophylaxis against osteoporosis and cardiovascular disease and must be continued indefinitely to maintain the protection, it is important that we reach unanimity on the effects of long-term use.

The proposed study is warranted in that it addresses the shortcomings some previous studies incurred either by design or as a consequence of being dated. In this analysis, it has been possible to take full account of various confounding factors. Furthermore, the risk accrued by women who have been taking HRT for long periods of time or in combination with progestin can now be assessed with greater precision as the numbers are more substantial. This study was undertaken in hopes of improving on certain existing data and corroborating other, with the knowledge that in epidemiology, replication is integral to forming definitive statements.

1.2 Objectives

This thesis is analytic in nature, involving postmenopausal women only, with the following primary objectives:

- To corroborate previous findings regarding the association between the risk of breast cancer and ever use of HRT.
- To examine the risk of breast cancer in relation to different types of HRT (i.e. estrogen only, estrogen-progestin).
- To re-evaluate the effects of duration of HRT use on the risk of breast cancer.
- To determine whether breast cancer odds ratios are influenced by time since discontinuation of HRT use.
- To determine whether the use of HRT is subject to a latent effect.
● **Secondary objective:** to investigate possible interactions between HRT and other known risk factors for breast cancer such as age, body size, benign breast disease, type of menopause, ovarian status, family history of breast cancer, smoking status and alcohol consumption.

1.3 Descriptive Epidemiology

1.3.1 Burden of Disease

Breast cancer is the most frequently diagnosed malignancy in Canadian women, accounting for 29.8% of all female incident cases (National Cancer Institute of Canada (NCIC), 1999). In 1999, an estimated 18,700 women will be diagnosed with breast cancer in Canada. The estimated age-standardized incidence rate is 105 per 100,000 (NCIC, 1999).

Relative to other types of cancer, breast cancer is considered to have a very good prognosis with a ratio of deaths to new cases at under 30% (NCIC, 1999). Nevertheless, given the burden of the disease, an estimated 5,400 deaths in 1999 ranks breast cancer second only to lung cancer as a cause of cancer death among Canadian women (NCIC, 1999). The estimated age-standardized mortality rate is 28 per 100,000 (NCIC, 1999).

1.3.2 Trends

There has been a steady increase in the incidence of breast cancer since 1984. Between 1987 and 1994, breast cancer increased at 0.7% per year, although the rate of increase is currently declining somewhat (NCIC, 1999). This time trend is driven by increasing rates among women over 50 years old; incidence rates among women under 50 years old have remained steady (Health Canada, 1999).
Overall, breast cancer mortality declined an average of 1.2% from 1987 to 1996, although most of this reduction is attributed to a decline in risk after 1990 among women ages 50-69 (NCIC, 1999). The most marked reduction in mortality has been seen among women ages 60-69 years, in whom the mortality rate has dropped by 15% since 1990 (Gaudette et al., 1996).

There is some international geographic variation in incidence, with higher rates in Western Canada and lower rates in the Atlantic region (Health Canada, 1999). Estimated age-standardized incidence and mortality rates for Ontario are identical to the national average for 1999 (NCIC, 1999). The rates in the United States are comparable to the aforementioned Canadian statistics (Merrill & Feuer, 1996). The incidence of breast cancer is more than twice as high in Canada and the United States as it is in Asia and Africa (Parkin et al., 1997).

1.3.3 Age

The probability of developing breast cancer increases steadily with increasing age (Health Canada, 1999). Seventy-seven percent of women with breast cancer are over age 50 (NCIC, 1999). Among women aged 30, the probability of developing breast cancer within the next five years is 1.5 in 1,000. The probability increases to 9.2 in 1,000 for women aged 50. By aged 80, the probability reaches a level of 15.5 in 1,000 (Health Canada, 1999). The age-related increase in breast cancer incidence is much steeper in women of premenopausal age as opposed to postmenopausal ages (Brinton & Schairer, 1993).
Chapter 2
Literature Review

2.1 Prescribing of HRT

Hormone replacement therapy was first approved by the U.S. Food and Drug Administration in the 1940's, although it did not become widely used until the 1960's (Brett and Madans, 1997). From the 1960’s until 1980, women were given estrogen alone and incurred an increased risk of endometrial cancer (Persson, 1985). Since the early 1980’s, estrogen has been prescribed with progestin (a synthetic form of progesterone) to offset the cancer-causing effect on the uterine lining. Thus, modern types of HRT include estrogen alone (hereinafter ERT) and estrogen and progesterone in combination (hereinafter CRT). (The acronym HRT will be used to designate any one or both of the aforementioned hormone replacement therapy types, ERT and CRT.)

According to IMS Health, a source of pharmaceutical information, there were approximately 7,888,500 prescriptions dispensed for HRT in Canada in 1998. More and more prescriptions are being filled as baby boomers reach menopause; in 1994, the number of prescriptions dispensed for HRT was 5,338,847, thus, the figure for 1998 represents almost a 50% increase since 1994 (Dorothy Rhodes, personal communication). The most commonly prescribed form of hormone replacement therapy is the pill form. Estrogen pills are taken every day throughout the month or for the first 25 days of the month only. Those who have not had hysterectomies usually take progestin pills as well for 10 to 14 days of the pill cycle although this can cause monthly bleeding. If both hormones are taken every day throughout the month, most women cease bleeding after three to six months. Another option is the patch, which is attached to the body with an adhesive and contains estrogen in gel form which is released
into the body. Progestin pills can be taken along with the patch, as warranted. A third option is estrogen cream. Older therapies include estrogen injections and sub-dermal implants.

Hormone replacement therapy comes in many different preparations. The most common preparations used today are conjugated equine estrogens, the best known brand of which is Premarin®. Other drugs approved for HRT contain different types of synthetic estrogens, including estradiol, dienestrol, esterified estrogen and estropipate (Risch & Howe, 1994). There are at least three forms of estrogen produced by the human body, estrone (E1), estradiol (E2) and estriol (E3), in the approximate ratio of 7:3:90 (Schlesman & Robinson, 1997). E3 is a combination of E1 and E2 and is much less potent. Conjugated estrogens consist of E1 (75-80%), E2 and other forms of estrogen derived from the urine of pregnant mares (Wyeth-Ayerst Company, 1998). The other HRT preparations consist of combinations of synthetic forms of E1, E2 or E3 or natural E1, E2 or E3, derived from plants. Only one relatively obscure preparation mimics the endogenous estrogen ratio. It is known as “Triple estrogen” and consists of all three separate estrogens – E1, E2 and E3 – all of which are derived from the wild yam plant. Triple estrogen is not available at standard pharmacies (Dorothy Rhodes, personal communication). The active ingredient in progestin is medroxyprogesterone, the most common brand name of which is Provera®.

In the US and Canada, over 90% of HRT prescriptions are for conjugated estrogens (Bergkvist & Persson, 1996; Risch & Howe, 1994) but in Europe, as many as 56% are for estradiol (Bergkvist & Persson, 1996). The doses prescribed also vary, i.e. 0.3 milligrams (considered “low dose”), 0.625 milligrams (standard dose) or 1.25 mg/day. Progestin is prescribed in doses of 2.5 to 5 mg.
Physicians are prescribing HRT in the belief that it will improve women’s quality of life after menopause and increase lifespan. Women who take hormone replacement therapy for 10 years have been found to have a 37% reduced risk of dying from all causes over an 18 year period (Grodstein et al., 1997). This decrease is primarily because of fewer deaths from heart disease among users.

HRT has been prescribed on a long-term basis for women at risk of cardiovascular disease, the leading cause of death in women past menopause. Estrogen has been found to increase the level of high-density lipoprotein cholesterol (a low level of which is a predictor of heart disease) by 33% (Vadlamudi et al., 1998). The risk of stroke is estimated to be 32% lower and the risk of heart disease 53% lower, for women who take HRT as compared with women who do not (Grodstein et al., 1997). Recently, some doubt has been cast on the issue of whether women who already have heart disease can benefit from HRT; in a recent study, women taking supplements suffered a greater number of heart attacks during the first year, albeit fewer heart attacks in subsequent years (Hulley et al., 1998). HRT is also prescribed on a long-term basis to prevent osteoporosis. In addition, short-term use of HRT is sufficient to alleviate menopausal symptoms such as hot flashes, mood swings, flushing, night sweats and vaginal dryness (Hunt & Vessey, 1987).

Emerging benefits of HRT underscore its prophylactic potential. Taking estrogen may reduce the risk of Alzheimer’s disease by 54% or delay the onset of symptoms (Waring et al., 1999). HRT may also reduce the risk of colon cancer (Grodstein et al., 1999).

Women who have a family history of breast cancer, liver disease, endometrial cancer, stroke, blood clots or unexplained vaginal bleeding are usually advised not to take the drug, although
not all of these characteristics are definite contraindications to HRT. Known drawbacks of HRT use include a three times greater risk of potentially fatal blood clots, side effects such as tender breasts, fluid retention, swelling, moodiness and cramps associated with progestin and the possibility of an increasing risk, still unconfirmed, of breast cancer (Waldman, 1998).

2.2. HRT and Breast Cancer Risk

2.2.1 Epidemiologic Studies

For the purposes of this review, only studies that have been published during 1990, or later, will be cited. These more recent studies represent the current standards of epidemiological study. Earlier studies focussed on populations of women who were using HRT primarily for acute menopausal symptoms and whose estrogen doses and preparations varied more than they do now. With few exceptions, early studies did not include substantial numbers of women with long-term use or combination use. At least 20 studies – 10 case control and 10 cohort – examining the relationship between HRT and breast cancer risk have been published since 1990.

*ever use of HRT*

Table 1 summarizes the 17 recent studies that presented risk estimates for ever use. Twelve of these studies had reassuring results with risk estimates hovering around unity. while 2 case-control studies and 3 cohort studies reported a significant increase of about 20-35% (Colditz et al., 1990; Kaufman et al., 1991; Risch & Howe, 1994; Colditz et al., 1995; Tavani et al., 1997). The three stages of follow-up from the Nurses’ Health Study are difficult to compare as the results are based on differing criteria; in the first paper, Colditz et al. (1990)
reported a relative risk of 1.36 (95% CI=1.11-1.67) among current users of HRT, in a second follow-up the relative risk was 1.08 (95% CI=0.96-1.22) for ever users of HRT (Colditz et al., 1992), and in a later follow-up the risk was similar to that from the first report (RR=1.32, 95% CI=1.14-1.54), but in this case, among ever users of ERT (Colditz et al., 1995).

Table 1. Selected studies examining the relation between ever versus never use of HRT*, irrespective of progesterone content

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Design</th>
<th>Source of subjects</th>
<th>RR* for ever use</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colditz et al. (1990)</td>
<td>USA</td>
<td>Cohort</td>
<td>NHS*</td>
<td>1.36*</td>
<td>1.11-1.67</td>
</tr>
<tr>
<td>Kaufman et al. (1991)</td>
<td>USA &amp; Canada</td>
<td>Case control</td>
<td>Hospital</td>
<td>1.2b</td>
<td>1.0-1.4</td>
</tr>
<tr>
<td>Palmer et al. (1991)</td>
<td>Canada</td>
<td>Case control</td>
<td>Community</td>
<td>0.9b</td>
<td>0.6-1.2</td>
</tr>
<tr>
<td>Colditz et al. (1992)</td>
<td>USA</td>
<td>Cohort</td>
<td>NHS</td>
<td>1.08</td>
<td>0.96-1.22</td>
</tr>
<tr>
<td>Yang et al. (1992)</td>
<td>Canada</td>
<td>Case control</td>
<td>Community</td>
<td>1.0</td>
<td>0.8-1.3</td>
</tr>
<tr>
<td>Persson et al. (1992)</td>
<td>Sweden</td>
<td>Cohort</td>
<td>Community</td>
<td>1.0b</td>
<td>0.9-1.1</td>
</tr>
<tr>
<td>Weinstein et al. (1993)</td>
<td>USA</td>
<td>Case control</td>
<td>Community</td>
<td>1.14</td>
<td>0.84-1.40</td>
</tr>
<tr>
<td>Risch &amp; Howe (1994)</td>
<td>Canada</td>
<td>Cohort</td>
<td>Health Plan</td>
<td>1.33b</td>
<td>1.11-1.59</td>
</tr>
<tr>
<td>Schairer et al. (1994)</td>
<td>USA</td>
<td>Cohort</td>
<td>BCDDP*</td>
<td>1.0b</td>
<td>0.9-1.2</td>
</tr>
<tr>
<td>Colditz et al. (1995)</td>
<td>USA</td>
<td>Cohort</td>
<td>NHS</td>
<td>1.32b</td>
<td>1.14-1.54</td>
</tr>
<tr>
<td>Stanford et al. (1995)</td>
<td>USA</td>
<td>Case control</td>
<td>Community</td>
<td>0.9b</td>
<td>0.6-1.1</td>
</tr>
<tr>
<td>Newcomb et al. (1995)</td>
<td>USA</td>
<td>Case control</td>
<td>Community</td>
<td>1.05</td>
<td>0.93-1.18</td>
</tr>
<tr>
<td>Schuurman et al. (1995)</td>
<td>The Netherlands</td>
<td>Cohort</td>
<td>Community</td>
<td>0.99</td>
<td>0.68-1.43</td>
</tr>
<tr>
<td>La Vecchia et al. (1995)</td>
<td>Italy</td>
<td>Case control</td>
<td>Hospital</td>
<td>1.2</td>
<td>0.9-1.5</td>
</tr>
<tr>
<td>Folsom et al. (1995)</td>
<td>USA</td>
<td>Cohort</td>
<td>Community</td>
<td>1.23</td>
<td>0.99-1.55</td>
</tr>
<tr>
<td>Persson et al. (1997)</td>
<td>Sweden</td>
<td>Cohort</td>
<td>Community</td>
<td>0.5b</td>
<td>0.3-1.0</td>
</tr>
<tr>
<td>Tavani et al. (1997)</td>
<td>Italy</td>
<td>Case control</td>
<td>Community</td>
<td>1.2</td>
<td>1.0-1.4</td>
</tr>
</tbody>
</table>

* HRT indicates hormone replacement therapy; RR, relative risk; NHS Nurses' Health Study; BCDDP, Breast Cancer Demonstration and Detection Program

a Current use only

b Estrogen only

A number of meta-analyses have been performed indicating that ever use of HRT does not increase a woman’s risk of developing breast cancer (Dupont & Page, 1991; Steinberg et al., 1991; Colditz et al., 1993b). In the most comprehensive meta-analysis on the subject to date, investigators at Oxford University collected and reanalyzed data from 51 epidemiologic studies. The meta-analysis includes data on more than 52,000 women with breast cancer and 100,000 women without, thus representing 90% of the existing data on HRT and breast
cancer risk (Collaborative Group, 1997). They found a 14% increase in the risk of breast cancer associated with ever use of HRT (Collaborative Group, 1997).

duration of HRT use

Short term use of HRT (i.e. less than 10 years) has not been associated with any overall increased risk of breast cancer (Steinberg et al., 1991). Table 2 summarizes the 16 recent studies that presented risk estimates for long-term HRT use (i.e. greater than or equal to ten years).

Table 2. Selected studies reporting on the risk of breast cancer in relation to duration of HRT* use, irrespective of progesterone content

<table>
<thead>
<tr>
<th>Reference</th>
<th>Longest reported duration of use (yrs)</th>
<th>RR*</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colditz et al. (1990)</td>
<td>&gt;15</td>
<td>1.19a</td>
<td>0.6-2.2</td>
</tr>
<tr>
<td>Kaufman et al. (1991)</td>
<td>&gt;15</td>
<td>0.9b</td>
<td>0.4-2.1</td>
</tr>
<tr>
<td>Palmer et al. (1991)</td>
<td>&gt;15</td>
<td>1.5b</td>
<td>0.6-3.8</td>
</tr>
<tr>
<td>Yang et al. (1992)</td>
<td>&gt;10</td>
<td>1.6b</td>
<td>1.1-2.5</td>
</tr>
<tr>
<td>Weinstein et al. (1993)</td>
<td>&gt;5</td>
<td>0.88</td>
<td>0.53-1.44</td>
</tr>
<tr>
<td>Risch &amp; Howe (1994)</td>
<td>7% increased risk per year*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schairer et al. (1994)</td>
<td>&gt;20</td>
<td>1.1b</td>
<td>0.8-1.5</td>
</tr>
<tr>
<td>Colditz et al. (1995)</td>
<td>&gt;10</td>
<td>1.46a</td>
<td>1.20-1.76</td>
</tr>
<tr>
<td>Stanford et al. (1995)</td>
<td>&gt;20</td>
<td>1.0b</td>
<td>0.5-2.0</td>
</tr>
<tr>
<td>Newcomb et al. (1995)</td>
<td>&gt;15</td>
<td>1.11</td>
<td>0.87-1.43</td>
</tr>
<tr>
<td>Schuurman et al. (1995)</td>
<td>&gt;5</td>
<td>0.9</td>
<td>0.4-2.1</td>
</tr>
<tr>
<td>La Vecchia et al. (1995)</td>
<td>&gt;5</td>
<td>1.5</td>
<td>0.8-2.6</td>
</tr>
<tr>
<td>Persson et al. (1997)</td>
<td>&gt;10</td>
<td>2.1</td>
<td>1.1-4.0</td>
</tr>
<tr>
<td>Tavani et al. (1997)</td>
<td>&gt;5</td>
<td>1.3</td>
<td>0.8-2.0</td>
</tr>
<tr>
<td>Magnusson et al. (1999)</td>
<td>&gt;10</td>
<td>2.43</td>
<td>1.79-3.30</td>
</tr>
<tr>
<td>Schairer et al. (1999)</td>
<td>2% increased risk per yearb</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*HRT indicates hormone replacement therapy; RR, relative risk; CI, confidence interval
a Current use only
b Estrogen only

Thirteen of the studies reported point estimates that exceeded 1.0. In 4 of these 13 studies, significance was attained (Yang et al., 1992; Colditz et al., 1995; Persson et al., 1997; Magnusson et al., 1999). Propitiously, the longest reported duration of use in each of these 4 studies was greater than or equal to ten years, thus comparisons can be made; the risk estimates ranged from 1.46-2.43 (Yang et al., 1992; Colditz et al., 1995; Persson et al., 1997; Magnusson et al., 1999). The results from the
Nurses’ Health Study (NHS) indicated that an increased risk among long-term users is confined to current users; accordingly results were stratified by current/former use. The 1995 NHS follow-up showed a significant increase in risk for ten years of use among current users (RR=1.46, 95% CI=1.20-1.76) (Colditz et al., 1995). In the 1990 NHS follow-up the point estimate relating 15 years of use to breast cancer risk, relative to non users, was 1.19, but the confidence interval was quite wide (95% CI= 0.6-2.2) (Colditz et al., 1990).

Only 2 of these studies found a trend with increasing duration (Risch & Howe, 1994; Schairer et al., 1999). Risch & Howe (1994) observed a 7% increase in risk for every 252 tablets used which corresponds to just under one year of use. Similarly, Schairer et al. (1999) found a linear relationship between duration of use and breast cancer risk (2% increased risk per year). Two studies reported p- values for trend; both of which were non-significant (Schuurman et al., 1995; La Vecchia et al., 1995). One cannot rule out the possibility of an effect after 10 years in studies where the highest category of duration was reported as five or more years (Weinstein et al., 1993; Schuurman et al., 1995; La Vecchia et al., 1995; Tavani et al., 1999).

The Oxford researchers, in their collaborative meta-analysis, found that the risk of breast cancer increased by 2.3% (95% CI=1.1%-3.6%; p=0.0002) for each year of HRT use and that there was little heterogeneity between studies (Collaborative Group, 1997). They also found an absence of an increase in relative risk in past users (79% of whom had used HRT for less than 5 years). Five years or more after cessation of use the overall relative risk was 1.07 (95% CI=0.97-1.18).
**estrogen dose and preparation**

Data on the risk of breast cancer according to type or dose of estrogen are scarce. Brinton et al. (1986) have associated estradiol use with a higher risk of breast cancer (RR=2.0) compared with use of conjugated estrogens (RR=1.1). With respect to dose of estrogen, results from a meta-analysis indicated that doses of conjugated estrogens of 1.25 mg/day may confer a greater risk than doses of ≤0.625 mg/day, although heterogeneity between studies precludes firm conclusions (Dupont & Page, 1991). In contrast, the Oxford researchers found no variation in risk according to either the type or the dose of estrogen (Collaborative Group, 1997).

**risk by estrogen alone versus estrogen plus progestin**

Table 3 lists recent studies which examined the effect of sequential addition of a progesterone. It is most constructive to compare risk estimates (ERT vs. CRT) within a particular study as they would be based on the same population and the same variable definitions, and would be subject to the same biases. Furthermore, the risk estimates relative to each other are what is important rather than the individual estimates, *per se*, because the issue here is whether combination therapy should be used in lieu of estrogen alone.

Point estimates relating the risk associated with ever use are consistently higher for CRT use, relative to ERT use, with the exception of the study by Palmer et al. (1991). Five studies reported risk estimates that were significantly above one for CRT. Three of these five studies represent instances where the risk estimate was not significantly above one for ERT use, but the corresponding CRT risk estimate was (Persson et al., 1992; Yang et al., 1992; Schairer et al., 1994).
Table 3. Selected studies providing breast cancer risk estimates for ever and long-term use, by type of HRT*

<table>
<thead>
<tr>
<th>Reference</th>
<th>ERT*</th>
<th>CRT*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR* ever use (95% CI)</td>
<td>Duration: (yrs)</td>
</tr>
<tr>
<td>Kaufman et al. (1991)</td>
<td>1.2</td>
<td>&gt;15 : 0.9</td>
</tr>
<tr>
<td>Palmer et al. (1991)</td>
<td>0.9</td>
<td>&gt;15 : 1.5</td>
</tr>
<tr>
<td>Colditz et al. (1991)</td>
<td>1.42a</td>
<td>&gt;15 : 2.0</td>
</tr>
<tr>
<td>Persson et al. (1992)</td>
<td>1.0</td>
<td>&gt;10 : 1.6</td>
</tr>
<tr>
<td>Yang et al. (1992)</td>
<td>1.0</td>
<td>&gt;10 : 1.6</td>
</tr>
<tr>
<td>Risch &amp; Howe (1994)</td>
<td>1.33</td>
<td>7% increased risk/year</td>
</tr>
<tr>
<td>Schairer et al. (1994)</td>
<td>1.0a</td>
<td>1.1</td>
</tr>
<tr>
<td>Colditz et al. (1995)</td>
<td>1.32a</td>
<td>&gt;20 : (0.8-1.5)</td>
</tr>
<tr>
<td>La Vecchia et al. (1995)</td>
<td>1.3</td>
<td>&gt;15 : 1.65</td>
</tr>
<tr>
<td>Newcomb et al. (1995)</td>
<td>0.97</td>
<td>&gt;15 : 1.02</td>
</tr>
<tr>
<td>Stanford et al. (1995)</td>
<td>0.9</td>
<td>&gt;5 : 0.8</td>
</tr>
<tr>
<td>Persson et al. (1997)</td>
<td>0.5</td>
<td>&gt;10 : 1.3</td>
</tr>
</tbody>
</table>

* HRT indicates hormone replacement therapy; ERT, estrogen replacement therapy; CRT, combination (estrogen and progestin) replacement therapy; RR, relative risk;

Seven studies addressed the continuous use of combined hormone replacement therapy. In all cases, heterogeneity in the results according to type of HRT was not significant. Two of the studies failed to find any appreciable difference in risk estimates for long-term ERT use versus long-term CRT use (Schairer et al., 1994; Newcomb et al., 1995). Two studies
reported risk estimates associated with long-term CRT use that were elevated in the order of 40% above the estimate for long-term ERT users (Risch & Howe, 1994; Stanford et al., 1995). Due to the small numbers of long-term users, the estimates did not reach significance. Three studies suggest that risk of breast cancer is elevated with the addition of progestin (Kaufman et al., 1991; Persson et al., 1997; Schairer et al., 1999). Most markedly, Persson et al. observed that the risk associated with CRT use was twice that for ERT use, although not significantly different.

In the combined reanalysis of epidemiologic studies, current use of CRT with a duration of use of five years or more was associated with a higher risk of breast cancer (RR=1.53; 95% CI=0.8-2.92) than was current use of ERT of five years or more (RR=1.34; 95% CI=1.12-1.59) (Collaborative Group, 1997). This difference was not statistically significant as the numbers of women with long durations of CRT use were insufficient (58 cases, 86 controls).

**HRT and breast cancer mortality**

The largest and most complete examination of breast cancer mortality associated with long-term use of postmenopausal hormones comes from the Nurses’ Health Study (Grodstein et al., 1997). Over one hundred and twenty thousand women were questioned every two years, from 1976 until 1992, regarding their use of HRT (among many other questions) and deaths were documented to 1994. During the first ten years of hormone use, women who used postmenopausal hormones had a 24% reduced risk of death from breast cancer, compared with never users. Dramatically, mortality due to breast cancer rose 43% in women who took postmenopausal hormones for more than ten years, relative to women who had never taken them. By questioning women every two years, this was the only study to overcome the
potential bias caused by the discontinuation of hormone use after a breast cancer diagnosis; removing the stimulus may affect the prognosis.

**HRT and histologic type of breast cancer**

Recent results from the Iowa Women's Health Study, a cohort study including over 37,000 women, indicate that there is little connection between use of HRT and the risk of the most aggressive types of cancer – invasive ductal or lobular – which account for 85 to 90% of all breast cancers (Gapstur et al., 1999). The investigators did find an association between HRT use and the risk of less common types of breast cancer which have a more favourable prognosis, respond well to treatment and are less likely to metastasize (i.e., medullary, papillary, tubular and mucinous tumors). Women who had taken HRT for five or fewer years had an increased risk of these invasive carcinomas with favourable histology over those who had not taken HRT (RR=1.81, 95% CI=1.07-3.07), and those who had used it for five years or longer had an even further increased risk of such cancers (RR=2.65, 95% CI=1.34-5.23) (Gapstur et al., 1999). Findings by Newcomer et al. (1999) suggest that the adverse effect of HRT is restricted to increased development of lobular carcinomas only (OR=3.1, 95% CI=0.8-2.1).

**subgroup effects**

Certain factors may increase susceptibility to the effects of HRT by acting either synergistically or antagonistically with estrogen. The relationship between breast cancer, HRT and the combination of various third variables is unclear. Multiplicative interactions
have been suggested between estrogen use and each of ovarian/menopausal status, oral contraceptive use, obesity, alcohol consumption, family history, smoking status and age.

The interaction of estrogen use with ovarian or menopausal status has been evaluated in several studies. There is some evidence of higher risks associated with estrogen use among women who have had a bilateral oophorectomy (Hoover et al., 1981; Wingo et al., 1987), while other studies, in contrast, have found an elevated risk among women whose menopause was not brought on by oophorectomy (Ross & Paganini-Hill, 1980; Hulka et al., 1982) and still others have shown that type of menopause does not alter the effects of HRT (Palmer et al., 1991; Kaufman et al., 1991). These inconsistent results may in part be due to differing subgroup definitions; some studies have focussed on ovarian status at menopause, others have looked at ovarian status at diagnosis, while others have only differentiated between those with a natural or a surgical menopause.

It has been hypothesized that the combined dose of estrogen received by women who have taken both oral contraceptives and HRT may thrust the level of estrogen exposure above a certain biologic threshold for producing breast-cancer-promoting effects. As of yet, there has been no concrete evidence of a combined effect (Brinton & Schairer, 1993).

A few studies have assessed HRT effects by body weight under the rationale that the level of serum estrogen among obese postmenopausal women is enhanced through increased conversion of androgens in fat tissue to estrogens (Pike et al., 1993) and that a critical level of circulating estrogen may be exceeded. There was a dichotomy in the results; as reviewed by Brinton & Schairer (1993), three studies found an enhanced effect of estrogen use among obese women and three studies found a diminished effect. More recently, the large meta-
analysis conducted by the Oxford investigators addressed each of these potential effect modifiers. They found that the increasing risk of breast cancer associated with long-term current or recent use was more pronounced among women with lower body mass index (Collaborative Group, 1997). There was no significant variation in the results according to any of the other variables.

In a randomized clinical trial designed to determine if moderate alcohol consumption modifies the biologic effects of ERT among postmenopausal women, researchers found that when postmenopausal women taking ERT drank the equivalent of just half a glass of wine, the levels of circulating estradiol nearly doubled, on average. After a drink comparable to three glasses of wine, estrogen surged more than threefold. Among women who were not on ERT, alcohol did not significantly alter estradiol levels (Ginsburg et al., 1996). A cohort study did report a significant interaction between alcohol intake and ever use of noncontraceptive estrogen, with alcohol exacerbating the adverse effects of estrogen (Gapstur et al., 1992). An additional study which focused on long-term estrogen use among postmenopausal women in the Nurses’ Health study failed to find a statistically significant interaction between alcohol and hormones (Chen & Colditz, 1999).

Several studies have examined the potential interaction of estrogen use with family history of breast cancer. There is discrepancy in the results: as reviewed by Brinton & Schairer (1993), five case-control studies showed higher risks associated with HRT among women with a positive family history of breast cancer, while six other case-control studies and one cohort study found no excess risk.
Smoking has been found to alter the metabolism of estradiol (Baron et al., 1990). The effect of HRT may therefore be modified by smoking, although one study which addressed this possibility did not observe a differential effect of HRT between smokers and non-smokers (Hulka & Schildkraut, 1992).

Evaluating age-specific effects of HRT is now of particular importance as women are taking HRT much beyond menopausal ages. Preliminary evidence suggested that the effects tend to increase with age (Brinton & Schairer, 1993). The latest follow-up from the Nurses’ Health Study indicated that the increase in the relative risk of breast cancer associated with five or more years of postmenopausal hormone therapy was greater for older women (Colditz et al., 1995). One analysis which included almost 6,000 cases and was devoted entirely to addressing age-specific effects of various measures of HRT found that age influenced many of the relationships (Tavani et al., 1997). Their data indicated that only women in the highest age group (65-74 years of age) experienced an excess risk of breast cancer associated with ever use of HRT. A significant trend in risk with duration was also observed only among women 65-74. The effects of age at and time since starting HRT and time since stopping, did not vary significantly by age. The Oxford Group incorporated the data from Brinton & Schairer (1993) and Colditz et al. (1995) in their re-analysis of most of the epidemiologic evidence available on the subject. While the results were not expressed in terms of the presence/absence of a significant interaction term, women between the ages of 50 and 70 had an estimated cumulative excess of six breast cancer diagnoses per 1000 women after ten years of use, compared to never users, while women under 50 years of age had no excess risk at all (Collaborative Group, 1997).
2.2.3 Biologic Mechanism

There are three necessary stages in the development of cancer: initiation, characterized by damage to the cell’s DNA; promotion, characterized by an increase in cell proliferation; and progression which, as with initiation, involves genotoxic effects although in this instance the damage facilitates invasion and metastasis and angiogenesis, among other things (Pike et al., 1993). Estrogen has been implicated as a promoter in this continuum; it can both increase mitotic activity above the baseline rate and activate genes that would normally not be dividing (Pike et al., 1993).

DNA is constantly incurring damage from a variety of sources, but this damage is not expressed as a gap or a mutation in the absence of cell division, because in the absence of rapid cell division, the DNA would be repaired before it is propagated (Pike et al., 1993). Excess cell division and proliferation allows for the expression of cells that have passed through the initiation stage, such as a damaged tumor suppressor gene, for example (Pike et al., 1993). Increased cell division also leads to an increased likelihood of random genetic errors which are a direct consequence of increased mitotic activity. Such mutation or translocation can thus lead to activation of oncogenes (Cohen & Ellwein, 1990; Ames & Gold, 1990).

Specifically, estrogens have been found to enhance the production of stimulatory and inhibitory growth factors (EGF, TGF-α, TGF-β) and insulin-like growth factors (IGF-I and –II) which both, in turn, act at the level of progression (Lupulescu, 1995) as well as the production of oncogenes (fos, myc) which regulate normal cell growth. These major effects of estrogens are mediated through receptors for estrogen which respond to the hormone's
growth stimulating effects (Pike et al., 1993). Until recently, it was thought that only one type of estrogen receptor – now called alpha (α) – existed but a second estrogen receptor, beta (β), has been discovered. Alpha receptors have been found primarily in the uterus and mammary gland. Beta receptors are generally nearly absent in cells were α abounds. Beta receptors predominate in the ovaries, testes, lungs, kidneys, intestines, bladder, colon, as well as osteoclast cells of the bone – areas where the α receptor is scarce (Kuiper et al., 1998; Vidal et al., 1999). Blood vessels are one of the few areas rich in both α and β receptors (Register & Adams, 1998). Both α and β are capable of binding with estradiol but they differ in their ability to bind with other estrogens. The beta receptor, for example is much more efficient at binding with genistein, a plant estrogen (Miodini et al., 1999). It is not yet known whether α and β activate different genes within the same tissue. The presence of α and β receptors throughout the body likely explain the wide-spread effects of estrogen.

While the effects of estrogen are mediated through estrogen receptors, it is an up-regulated level of these receptor proteins which leads to the designation of an estrogen receptor-positive (ER+) tumor (Habel & Stanford, 1993). As reviewed by Habel & Stanford (1993), no clear pattern emerges when considering all of the studies which have examined the association between hormone replacement therapy and ER status, although current assays rely on antibodies that only recognize estrogen receptor α.

There are also progesterone receptors which mediate the effect of progesterone. The effect of progesterone is a subject of debate. Although, transcriptional activation of c-fos and c-myc have been observed in the presence of progestins (Musgrove & Sutherland, 1994), the full
range of effects is not well defined and it is not known whether progestins stimulate or inhibit growth. The interactive effects between estrogen and progesterone are also not known; progestins might have an antiestrogenic effect or they may act synergistically with estrogen (Stanford & Thomas, 1993). If they do give protection against breast cancer, the mechanism is not the same as that in the endometrium (Gorins & Denis, 1995). There is presently no direct evidence that progestins influence estrogen’s effects by regulating the level of estrogen receptors (Gorins & Denis, 1995).

Further evidence of the influence of exogenous hormones on breast tissue comes from the effects of antiestrogens like tamoxifen. Tamoxifen has been shown to help prevent a new or recurrent breast cancer by blocking the stimulating effects of natural estrogen on breast tissue (Fentiman, 1990). Early evidence shows a similar effect by a second designer estrogen, raloxifene (Cummings et al., 1999).

2.3 Estrogen related factors

exposure to ovarian hormones

Many risk factors relate to the lifetime activity of the ovaries. The risk of breast cancer increases when women start menstruating early. For every 2-year increase in the age at menarche, the risk of breast cancer decreases by about 10% (Hsieh et al., 1990). Women who start menopause later fall into a higher risk category probably because of the consequent increased exposure to estrogen. For every 5-year delay in age at menopause, the risk of breast cancer increases by approximately 17% (Hsieh et al., 1990). Increasing parity has been found to be protective, likely due to a decreased number of ovulatory cycles. Compared to nulliparous women, the relative risk for parous women, relative to non parous women, is in
the range of 1.2 to 1.7 (Kelsey et al., 1993). Mounting evidence suggest that the number of births beyond the first, independent of the age at first birth, affects breast cancer risk. There is a trend of decreasing risk with increasing parity, with seven or more births reducing the risk to 0.6 (Kelsey et al., 1993). Hysterectomy alone (without bilateral oophorectomy) has not been associated with increased breast cancer risk (Brinton et al., 1988; Schairer et al., 1997; Irwin et al., 1988) and may even decrease risk (Kreiger et al., 1999). Incidentally, hysterectomy has been shown to advance the time of ovarian failure (Siddle et al., 1987). Unilateral oophorectomy has been associated with a potential increased risk (Brinton et al. 1988, Schairer et al., 1997). Conversely, bilateral oophorectomy has been shown to reduce the risk of breast cancer (Kreiger et al., 1999; Brinton et al., 1988; Schairer et al., 1997).

**breast feeding**

Data associating months of breast feeding with breast cancer risk are conflicting. A decreasing risk with increasing time breast feeding has been reported in at least eight studies while three studies found no such association (Kelsey et al., 1993). The effect of breast feeding may be related to ovarian activity because breast feeding induces the secretion of prolactin which in turn delays reestablishment of ovulation (Kelsey et al., 1993). The effect may instead be a direct result of increasing prolactin levels because prolactin has been shown to enhance the transformation of breast epithelium in animal studies (Bernstein & Ross, 1993).
**age at first full-term pregnancy**

Having a first full-term pregnancy in the early 20s reduces the risk of breast cancer. It has been speculated that an early full-term pregnancy desensitizes the breast to estrogen's effects by initiating further differentiation of breast cells (Kelsey et al., 1993).

**oral contraceptives**

Oral contraceptives (OC’s), which effectively suppress ovulation, lead to a drastic reduction in exposure to endogenous estrogens (Spicer & Pike, 1994). Exogenous estrogens in the OC itself raise circulating estrogen level. The net exposure to estrogen remains unchanged and no increased risk would be expected (Spicer & Pike, 1994).

The most definitive analysis on the issue of breast cancer risk and use of oral contraceptives comes from a reanalysis of the data from 54 epidemiologic studies on the subject (Collaborative Group, 1996). The Collaborative Group on Hormonal Factors in Breast Cancer found no long-term increase in breast cancer risk among ever users and a slightly increased risk of breast cancers among current users (RR=1.24, 95% CI=1.15-1.33). The risk gradually waned in the 10 years after cessation of use: 1-4 years after stopping the relative risk was 1.16 (95% CI=1.08-1.23); 5-9 years after stopping the relative risk was 1.07 (95% CI=1.02-1.13). Ten years after discontinuing, the increased risk subsided. Because the associations observed were unlike those typically found between carcinogens and cancer (where risk increases with duration or degree of exposure), the researchers postulated that the findings may – at least in part – be due to earlier diagnosis of breast cancer in women who have used oral contraceptives.
2.4 Lifestyle Factors

**body mass index**

Six of thirteen case control studies associated obesity with an increased incidence of breast cancer among postmenopausal women; cohort studies did not find any association (Hunter & Willett, 1993). The opposite effect was seen among premenopausal women with obesity leading to a decreased risk (Hunter & Willett, 1993). The dichotomy in the effects is attributed to the fact that excess adipose tissue leads to synthesis of estrogen and high levels of estrogen will disrupt the menstrual cycle and prevent ovulation in premenopausal women (Simpson & Zhao, 1995). In postmenopausal obese women this high level of endogenous estrogen has deleterious effect on breast tissue (Hunter & Willett, 1993). Taking into account the timing of weight gain, Kumar et al. (1995) linked weight gain from age 30 to a 23% increase in breast cancer risk, and a gain of 20 pounds was associated with a 52% increase.

**physical activity**

There is growing evidence that regular physical activity might help prevent breast cancer (Frisch et al., 1992; Bernstein et al., 1994). One study, involving more than 25,000 women in Norway found that women who exercised at least four hours a week had a 37 percent reduction in breast cancer risk relative to the least active women (Thune et al., 1997). Friedenreich et al. (1998), in a review based on 21 studies indicate that case-control studies typically report reduced odds ratios in the order of 25-30% for the most active women while several prospective studies failed to find evidence of a protective effect. There is evidence that physical activity during adolescence is associated with a reduction in subsequent breast cancer risk, although most studies inquired only about current exercise habits (Friedenreich
et al., 1998). Exercise may suppress total estrogen production by delaying menarche, reducing the frequency of ovulation and decrease the amount of abdominal fat (which produces estrogen) (Bernstein et al., 1994). Thus, timing of exercise may be critical.

**dietary fat**

Cohort studies have implicated high-fat diets as a cause of breast cancer. Japanese women – who, on average, have a lower fat intake, have a much lower incidence of breast cancer than North American women; when Japanese women migrate to a higher risk country such as North America and adopt a Western diet, they experience an increase in breast cancer rates (Haenszel et al., 1968; King et al., 1980).

Other epidemiologic studies have not all substantiated such ecologic studies. Wolk et al. (1998) found polyunsaturated fats to be harmful (although the association was not strong), but found that an increased consumption of monounsaturated fat was protective. Among women with the same total fat intake, those who ate 10 more grams of monounsaturated fat a day had a 50% reduction in risk of breast cancer. They found no association between breast cancer risk and saturated fat intake. Adding to the controversy, Holmes et al. (1999) reported no difference in the risk of breast cancer between those with a high-fat or a low-fat diet or between those with differing total fat intakes.

Dietary fat may influence estrogen levels which in turn alter breast density (Boyd et al., 1998a). When women reduced their dietary fat intake by approximately one-third, they decreased the area of dense breast tissue by 6.1% (Boyd, 1998a). Women whose breasts
consist of 60-75 percent dense tissue are four to six times more likely to develop breast cancer than women with no dense tissue (Boyd et al., 1998b).

**alcohol consumption**

A recent meta-analysis has shown that women who consume no more than one drink a day have a 9% increased risk of breast cancer compared to nondrinkers. This risk rises linearly with increasing alcohol intake but levels off at greater than 5 drinks per day. Women who consumed 2-5 drinks per day were 41% more likely to develop breast cancer. Comparable amounts of beer, wine and liquor yielded similar risk estimates (Smith-Warner et al., 1998).

**smoking**

Most studies have failed to establish any link between smoking and breast cancer (Rosenberg et al., 1984; London et al., 1989; Ewertz, 1990), but these studies did not take into account the possibility of individual differences in sensitivity to carcinogens. Fifty-five percent of white women produce a defective, slow-acting version of an enzyme, N-acetyltransferase (NAT2). This enzyme enables the body to detoxify carcinogens (specifically, aromatic amines) in cigarette smoke. Women with the defective gene are known as “slow acetylators”. Slow acetylators who smoked more than a pack of cigarettes a day incurred an increased risk of breast cancer (RR=4.4, 95% CI=1.3-14.8) The more heavily a woman with defective NAT2 genes smoked, and the earlier she had started, the higher her risk (Ambrosone et al., 1996).
2.5 Other Factors

family history

Having a mother, sister or maternal aunt who had breast cancer is a risk factor for breast cancer. There are two defective genes, BRCA1 and BRCA2, that are now known to account for some hereditary, familial breast cancer. There is also evidence that at least one more breast cancer gene exits (Serova et al., 1997). BRCA1 accounts for approximately 5% of all breast cancer cases (Foulkes & Narod, 1995), but its carriers have a 50% risk of developing breast cancer by age 50 and 86 percent by age 80 (Easton et al., 1995). BRCA2 accounts for less than 1% of all breast cancer cases and its penetrance is weaker than that of BRCA1 among women under 50 years of age; the risk of developing breast cancer by age 50 is 28% and by age 70 it is 84% (Ford et al., 1998).

ethnicity

Jewish women account for a disproportionate number of incident breast cancer cases attributed to a defective BRCA1 or BRCA2 gene. BRCA1 is found in 1% of Jewish women of Eastern and Central European origin (Struewing et al., 1997). BRCA2 is also found in 1% of Ashkenazi Jewish women, independent of BRCA1, but is extremely rare in the non-Jewish population (Roa et al., 1996). Taken together, about one out of 50 Ashkenazi Jewish women may have a gene that predisposes them to breast cancer.

height

Studies consistently report a modest association between attained height and breast cancer risk (Hunter & Willett, 1993). Analyses stratified by menopausal status showed a greater
increase in risk with increasing height among postmenopausal women with an uppermost threshold at 170 cm (Hunter & Willett, 1993).

**socioeconomic status**

Educational attainment and income are both indicators of socioeconomic status (SES). Both are strongly associated with the risk of breast cancer (Devise & Diamond, 1980). The impact of education level on breast cancer risk is thought to be confounded by underlying exposure to endogenous hormones as educated women often delay childbearing or have fewer children. Adjusting for reproductive variables greatly attenuates (although not to the point of disappearance) the relationship between high education level and the risk of breast cancer (Heck & Pamuk, 1997).

**history of benign breast disease**

Histologic changes in the epithelial cells of the mammary gland, classified as benign breast disease, are potential precursors for breast cancer (Bodian, 1993). Compared with women who received a biopsy specimen without proliferative changes, atypical hyperplasia is associated with a 2 to 5.3-fold increase in risk, while proliferative disease without atypia is associated with a 1.6 to 1.9-fold increase in risk (Bodian, 1993; Colditz, 1993a).

**2.6 Summary**

The evidence that estrogen acts as a promoter suggests an etiologic role for exogenous estrogen use in breast cancer. Despite the considerable number of epidemiologic studies, there is still uncertainty about many aspects of the association between HRT and breast
cancer. Until the collaborative reanalysis of the data from 51 studies was published, the issue of ever/never use was thought to be resolved in favour of no association; the Oxford Group, however, found an increased risk, prompting a revisitation of the issue. Relatively few studies have examined risk in terms of current/former use. Most notably, data from the Nurses’ Health study indicated that risk is confined to current users only. In terms of long-term use, overall, most studies have reported point estimates that exceed unity, but the highest reported durations vary, hampering comparisons, and the confidence intervals lack precision. As the number of long-term users increases, additional studies are warranted to readdress this issue. Mounting evidence suggests that CRT does not oppose the effects of estrogen, as it does in the uterus, but again, the numbers are small and only two significant estimates have been reported. Hormone effects may be modified by various breast cancer risk factors, but studies disagreed on which subgroups are at highest risk. Furthermore, many studies ran multivariate analyses allowing for a large number of potential confounders simultaneously, without confirming that each was indeed a confounder, so it was impossible to determine which variables need to be included. A comprehensive analysis was undertaken to add insight to each of these relevant issues.
Chapter 3
Methods

3.1 Study Design

3.1.1 Enhanced Cancer Surveillance (ECS) Project

The ECS Project is a population-based case-control study developed by the Cancer Bureau of the Laboratory Centre for Disease Control and the Provincial Cancer registries and funded by Health Canada under the Action Plan on Health and the Environment. A subset of the data collected from the Ontario component of the ECS project was used in this analysis. Cases comprised patients with a new diagnosis of one of fourteen specified cancer sites; a sex and age-matched population based control group was also identified. Information was gathered on residential, occupational, environmental and lifestyle risk factors for cancer using mailed questionnaires and telephone follow-up.

3.1.2 Case Definition & Ascertainment

Subjects were considered eligible if they were diagnosed between April 1, 1995 and March 31, 1996, with a new primary cancer of the breast, were between 20 and 74 years of age at the time of diagnosis and if they were a resident of Ontario at the time of diagnosis. Cases were selected based on the information reported in pathology reports submitted to the Ontario Cancer Registry and were therefore histologically confirmed. For each month of diagnosis, a random sample of eligible cases was selected from the total number of reports received by the registry. Breast cancer cases were further sampled by age; approximately 50% of the cases were under 49 years of age and 50% were 50 years of age or over. For this particular analysis, only postmenopausal women were included.
3.1.3 Control Definition & Ascertainment

Controls were selected from Ontario residents between the ages of 20 and 74. Controls were drawn from a geographically and temporally defined population; the sampling frame was based on the 1995 Ontario Ministry of Finance Property Assessment database which documents all residents of Ontario who had a property address in Ontario during the year 1995. The database contains surnames, given names and year and month of birth. Lists of Ontario residents, stratified by sex and five year age groups, were then compiled. (Age was calculated at January 1, 1996, being approximately half way through the period of case ascertainment.) The number of names needed to be sampled in each sex-age stratum was calculated as follows:

\[ 3 \times (\text{# of completed questionnaires required}) \times \frac{1}{\text{expected response rate}}. \]

Fourteen different cancer sites were ascertained as part of the Enhanced Cancer Surveillance study and breast cancer cases made up only a portion of the total number of cases. The above calculation was therefore repeated for each cancer site.

The number of controls ascertained for each sex-age stratum was determined by the limiting site i.e., the site that required the highest number of controls to achieve a 1:1 ratio (which in the younger age groups, was often breast cancer). For this analysis, a random sample of the controls was selected to yield a 1:1 case/control ratio within each five-year age stratum. The distribution of cases and controls by age is shown in table 4.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Frequency of cases</th>
<th>Frequency of controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-39</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>40-44</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>45-49</td>
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<td>65-69</td>
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<td>89</td>
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<tr>
<td>70-74</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>404</strong></td>
<td><strong>403</strong></td>
</tr>
</tbody>
</table>

*There were only 3 controls to sample from.*

Table 4. Age distribution
3.1.4 Physician Contact

Physicians were identified from pathology reports and were sent a form on which they were asked to provide the vital status of the patient, confirm the diagnosis, supply or verify the address and telephone number and give consent to contact the patient. If consent was withheld, the physician was asked to provide the reason. The physician could also decline to give or deny consent if he or she was no longer attending the patient, and was then asked to provide the name of the new physician. If the patient was deceased, for breast cancer cases, the next of kin was not contacted.

If no response was received from a physician within fourteen days after the request was mailed, telephone follow-up was initiated. Non-responsive physicians were mailed a letter giving them the opportunity to provide blanket consent for ECS to contact any of their patients (relieving them of the task of completing individual consent forms), indicate if they would prefer to continue receiving individual requests, or state that they would not participate in ECS in any way. Physicians choosing the last option were not contacted again. Their outstanding cases were switched to another physician identified from the Ontario Patient Information System (OPIS) files or from the hospital. If blanket consent was given, addresses and telephone numbers for the patients were obtained from OPIS or from the Medical Records departments of the hospital where they had been diagnosed. Since physician confirmation of diagnosis was not available, the pathology report was reviewed to ensure that the diagnosis was definitive. The Ontario Cancer Registry Information System (OCRIS) was checked for supporting reports.
3.1.5 Data Collection

Control subjects were ready to have questionnaires mailed immediately upon obtaining addresses from the Ministry of Finance database. Cases were eligible for questionnaire mailing when physician consent was received and an address was obtained, from the physician, the hospital where the person was diagnosed or treated, OPIS (for those treated at a Regional Cancer Centre) or Canada 411. Questionnaires and covering letters were sent in French as requested.

Postcard reminders were mailed one to two weeks after the initial questionnaire mail-out. Four weeks after the first questionnaire was mailed to the subject, another questionnaire and a reminder letter were mailed to those who had not yet responded. Delinquent subjects became eligible for follow up telephone calls six weeks after the questionnaire was first mailed. If they indicated that they did not intend to fill in the questionnaire, they were asked to provide a reason as to why. As questionnaires were received, respondents were called if clarification of responses was needed. Editors, as well as “clarification personnel”, were blinded with respect to case/control status.

3.1.6 Questionnaire

Participants completed a self-administered questionnaire; the comprehensive nature of the data collected provided an ideal resource for examining the influence of hormone replacement medication on the risk of breast cancer. All relevant information regarding primary variables, potential confounders and effect modifiers was available, specifically: use of estrogen and progestin preparations, menopausal status, reproductive history, dietary history, physical activity, oral contraceptive use, family history of cancer, body build,
ethnicity, smoking status, education level and income level. See Appendix A for the questionnaire from which the data used in this analysis were derived.

3.1.7 Personal Involvement on the Project

My role on the project was related to employment. Upon entering the M.Sc. Program, I was hired as a research clerk and worked part-time throughout my studies, under the direction of the Principal Investigator, Dr. Nancy Kreiger. My involvement included: ascertaining cases by retrieving pathology reports from the Ontario Cancer Registry, contacting physicians’ offices to follow-up on non-responses, preparing questionnaires and letters for mailing, performing data entry in the study management system as well as entering the questionnaires into the database. During the final year of the study, I took on the role of Project Coordinator and, in addition to the duties indicated above, I was responsible for ascertaining new cases applying the inclusion criteria, responding to participant and physician inquiries, monitoring progress on key milestones, maintaining the study management computer database and preparing progress reports describing response rates.

3.1.8 Response Rates

It is possible that the proportions of postmenopausal and premenopausal women who chose to participate in the ECS Project differ. A comparison of overall response rates might mask a response bias among the sample of postmenopausal women selected in this analysis. Menopausal status could not be obtained for those who did not respond, so age 50 was used as a proxy for menopause in stratifying response rates. A comparison of the response rates
between cases 50 and over and controls 50 and over will give an approximate indication of the response rate for the sample used in this analysis.

Of the women aged 50 or over, a total of 392 cases (86.5%) and 615 controls (77.7%) completed the questionnaire (Table 5). While controls were less likely to complete the questionnaire, the source of non-response is similarly distributed between cases and controls. One point three percent of cases and 0.2% of controls were too ill or depressed to participate; 2.2% of cases and 4.3% of controls were not interested; 8.0% of cases and 7.2% of controls gave no reason; 0.2% of cases and 3.2% of controls had a communication problem; 0.4% of cases and 2.8% of controls said the questionnaire was too complicated or personal; 1% of cases and 1.9% of controls were too busy; 0% of cases and 1% of controls gave other reasons.

The way in which the non-respondents did differ drastically was according to the ability to locate them. One hundred and forty-five (15.5%) controls could not be located, while only 12 (2.6%) cases could not be located. The response rate has been defined in two ways: Rate A = $\frac{\#\text{Questionnaires Received}}{\#\text{Questionnaires Sent}}$; Rate B = $\frac{\#\text{Questionnaires Received}}{\#\text{Questionnaires Sent} - \#\text{Unable to Locate}}$. Response rates calculated by excluding those who could not be located (response rate B) are preferred, for several reasons. First, for cases, there were many more avenues to explore in search of addresses, namely, physician records, hospital records and OPIS. Including those who could not be located in the response rate falsely alerts one to a bias that is merely an artifact of procedure. Secondly, it seems reasonable to exclude those who never had the opportunity to complete a questionnaire. There is a shortcoming inherent in response rate A. There were some cases for whom
Table 5. Response rates for all female breast cancer cases and all female controls

<table>
<thead>
<tr>
<th>Subject Status</th>
<th>Female Breast Cancer Cases</th>
<th>Female Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Age &lt;50</td>
</tr>
<tr>
<td>Ascertainment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Uninitiated¹</td>
<td>100</td>
<td>45</td>
</tr>
<tr>
<td>- No Physician</td>
<td>31</td>
<td>17</td>
</tr>
<tr>
<td>- MD Refusal</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>Too ill</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Not good candidate</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>No reason given/other</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>- Ineligible</td>
<td>57</td>
<td>25</td>
</tr>
<tr>
<td>Incorrect Dx² or Dx date or not ¹° cancer</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>Outside of age-range</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Resides outside of Ontario</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Case deceased</td>
<td>37</td>
<td>20</td>
</tr>
<tr>
<td>- Unable to Locate³</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>= Questionnaires Sent</td>
<td>836</td>
<td>468</td>
</tr>
<tr>
<td>- Case/ Control Refusal</td>
<td>148</td>
<td>87</td>
</tr>
<tr>
<td>Too ill, depressed</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Not interested</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>No reason given</td>
<td>94</td>
<td>57</td>
</tr>
<tr>
<td>Communication Problem</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Questionnaire too complicated/personal</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Too busy, no time</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>- Unable to Locate⁴</td>
<td>32</td>
<td>20</td>
</tr>
<tr>
<td>= Questionnaires Completed</td>
<td>764</td>
<td>392</td>
</tr>
<tr>
<td>Response Rate A (%)</td>
<td>80.7</td>
<td>77.2</td>
</tr>
<tr>
<td>Response Rate B (%)</td>
<td>83.6</td>
<td>80.6</td>
</tr>
</tbody>
</table>

¹ Study ended while cases still in progress.
² Dx indicates diagnosis.
³ No address, no questionnaire ever sent.
⁴ Incorrect address or unable to reach by phone.
⁵ Response Rate A=(Questionnaires Completed/Questionnaires Sent)*100
⁶ Response Rate B=(Questionnaires Completed/(Questionnaires Sent-Unable to Locate⁴))*100
we could not obtain any address at all (unable to locate\textsuperscript{3}, Table 5) and no questionnaire was ever sent. These subjects are not included in either response rate. It seems to be a quite arbitrary division to include in the denominator of the response rate those for whom there was an incorrect address and exclude those for whom there was no address at all. The main point in favour of using response rate B is that it includes people who could not be reached by phone who perhaps should be considered in the response rate (the database does not allow for distinction between those who could not be reached by phone and those who could not be reached by mail.)

3.2 Definition of Variables

3.2.1 Primary Variables

\textit{Date of diagnosis}

For cases, the date of diagnosis was obtained from the earliest pathology report available and corresponds to the date that the breast specimen was examined in the laboratory and determined to be cancerous.

\textit{Age}

Current age was defined as the age at diagnosis for the cases and the age as of Jan. 1, 1996 for the controls, as this was the midpoint of case ascertainment for the entire ECS study. (Age at diagnosis and current age will be used interchangeably.) Because there was a lag between diagnosis and data collection, corrections were made to censor the data at the age at diagnosis, for cases, or equivalently, for controls.
**Ever/Never use**

Women were asked to indicate if they had ever used hormone replacement medication for six months or more (shorter durations were considered biologically irrelevant). If women reported commencement of hormone use during the year of diagnosis, it was impossible to determine whether six full months of use had occurred before the diagnosis. In order to maintain a consistent definition of hormone use, any usage beginning at an age greater than or equal to the age of diagnosis was not considered.

**Type of hormone used**

Women indicated whether they had used ERT (estrogen alone) or CRT (estrogen and progesterone in combination). (Recall, the acronym HRT will be used to designate any one or both of the aforementioned hormone replacement therapies, ERT and CRT.) Simultaneous use of ERT and progesterone alone was recoded as use of CRT.

Only 6 women reported using progesterone alone (none of whom reported ever taking any other type of hormone). These numbers were too small to be considered separately and indications for their use likely preclude their proper combined classification with CRT and ERT users. Accordingly, they were classified as “never users” of HRT. Some women reported using some other type of hormone replacement medication, predominantly injections or vaginal cream. Injections consist of estrogen only, so these women were categorized as ERT users. While vaginal creams can help to prevent vaginal dryness, the dose of estrogen absorbed into the bloodstream is erratic and according to the AMA, the health benefits are not great (Slupik, 1997). This warrants the classification of women who used vaginal creams as never users. Some women were obviously unsure as to whether they
were taking ERT or CRT; these women indicated that they were taking some other type of hormone replacement medication and then gave the brand name of a medication which turned out to be either ERT or CRT. These women were reclassified as appropriate. One woman indicated that she was receiving estrogen from natural sources – she was classified as a non-user. Details on the specific dose were not solicited.

Current/Former use

Where applicable, the age at which each woman started and stopped taking each medication was ascertained to facilitate classification as a current or former user as well as calculation of duration of use and time since last/first use.

The questionnaire did not include a column for women to indicate whether they were still taking HRT. Hence, many women indicated that they did take HRT, filled in the age at which they started taking HRT and left the line for age stopped blank. Given the design of the questionnaire and the nature of the use of HRT (long term, prophylactic), it seems logical to infer that such women are still taking HRT. (Some women did specifically write “still taking” on the questionnaire.) A woman therefore was defined as a current user if the age stopped was greater than or equal to the current age or if she indicated an “age started” but left the “age stopped” blank (and did not specifically write “don’t know”, “?” or some equivalent, on the questionnaire.) Former users were all those who ceased taking a given type of HRT. For analyses not broken down by type of HRT, among women who used both ERT and CRT, former/current use was assessed by the preparation used most recently.
**Duration of use**

Duration of use was defined as the interval between the age at commencement of use and the age at cessation of use, in years. When the age was the same, duration of exposure was categorized as 0.5-1 year of use. For women who were assumed to be still taking HRT, current age was imputed as the age at cessation of use. Duration of use of HRT was arrived at by adding the duration of use of ERT and CRT. The designation “long-term use” has been used throughout to refer to women who used HRT for ten or more years. “Short-term use” indicates use of less than ten years duration.

**Time since first use**

Latency, measured as time since first use, was defined as the time interval between the age of the woman at first notation of hormone use and the current age. For women who used both ERT and CRT, time since first use of HRT was assessed by the preparation used first.

**Time since last use**

The time elapsed since cessation of use, equivalently the time since last use, was defined as the time interval between the age of the woman when she stopped taking hormones and her current age. For women who used both ERT and CRT, time since last use of HRT was assessed by the preparation used most recently.

**Menopausal status**

Women were classified as postmenopausal if their reported age at cessation of menses preceded the diagnosis date. Women whose menstruation ceased during the year of diagnosis
were classified as premenopausal and were excluded as it was not clear whether the cessation was a consequence of treatment. Menopausal status and age at menopause are sometimes unclear in women who started HRT use before their stated age at menopause since HRT may cause bleeding every month, much like having a menstrual period. This is more likely to happen when a woman takes estrogen for the first part of the cycle and adds progestin during the latter 10 to 14 days of the pill cycle. For women who took both hormones every day throughout the month (a more common regimen), bleeding generally stopped after three to six months. It was decided that a woman’s own account of her menopausal status would be used in the analysis.

3.2.2. Potential Confounders

*Categorization of variables*

Consult table 6 for the categorization of each of the variables. Categorization was performed according to established thresholds in the literature. When there was no biological basis for constructing categories, approximate quartiles were constructed based on the distribution among controls.

The definition of many of the potential confounders is intuitive, based on the variable name and the question from which it was derived. Such variables include age at menarche, never/ever oral contraceptive use, years of oral contraceptive use, height, marital status, income, ethnicity (Jewish, other) and physical activity. Clarification of the remaining variables follows.
Ovarian status

In order to address whether the cyclical production of hormones by the ovaries around the time of diagnosis is associated with the risk of breast cancer, postmenopausal women were further classified by ovarian status. The three categories defined were ovaries removed; ovaries intact but inactive; and ovaries intact and possibly active. Women were classified as having had their ovaries removed if, at any time prior to diagnosis, they had a bilateral oophorectomy (with or without hysterectomy). They were classified as having intact but inactive ovaries if they reported a natural menopause or cessation of menstruation because of irradiation of the ovaries (there were only 2 such women). For women who underwent hysterectomy and retained at least one ovary, ovarian function is often unknown. Some of these women were categorized as having intact, but inactive ovaries and others were categorized as having intact and possibly active ovaries. Colditz et al. (1990) have outlined a method for categorizing these women, adapted as follows: if their current age was equal to or above the 90th percentile of age at natural menopause for the controls (55 years), the ovaries were assumed to be inactive. Similarly, those whose current age was equal to or below the 10th percentile of age at natural menopause for the controls (40 years) were assumed to have active ovaries. Women whose age fell between 40 and 55 years were categorized as having missing ovarian status since ovarian function could not be elucidated with any great confidence.

Bilateral Oophorectomy

Bilateral oophorectomy (yes/no) is a variation of the previous variable, constructed in an effort to account for the relation of ovarian status to breast cancer risk. It was defined in the
same way as ovarian status with one change. In this case, no effort was made to differentiate between intact, but inactive ovaries, and intact but possibly active ovaries. These two categories were combined as bilateral oophorectomy, ‘no’.

Type of menopause

Type of menopause was defined as the event that caused the cessation of menstruation. Type of menopause, ovarian status and bilateral oophorectomy are all obviously closely related but it is not known which is the more important factor in determining risk of breast cancer associated with HRT use. The difference is that type of menopause only accounts for ovarian status at menopause and does not take into account surgeries following menopause; ovarian status and bilateral oophorectomy, however, take into account status as of diagnosis. Women were classified as having a natural menopause, menopause due to hysterectomy alone (retaining at least one ovary) or menopause due to hysterectomy and bilateral oophorectomy. There were no women whose menopause was due to bilateral oophorectomy without concomitant removal of the uterus. A few women indicated that they stopped menstruation due to physical or emotional stress. They were categorized as having a natural menopause. There were too few women whose menopause was due to radiation to be considered separately; they were classified as having an “other” type of menopause and were excluded from the analysis.

Age at menopause

Age at menopause was defined as the age at last menstrual period. Age at natural menopause includes only women who had a natural menopause. Age at menopause is related to both
HRT use and risk of breast cancer and is therefore a potential confounder. The pattern of HRT use is highly dependent on age at menopause; women with an early age at menopause were more likely to take postmenopausal hormones, and for longer durations, than those with a later age at menopause. In this study, for example, among women aged 55-59, for users with less than 5 years' use, the mean age at menopause is 49.7; for users with 5 or more years' use, it is 47.3 years of age. Furthermore, late age at menopause is associated with an increase in risk of breast cancer. The overall increase has been estimated to be 2.8% per year (Collaborative Group, 1997). If the increase is continuous over age at menopause, it might be important to account for age at menopause in small – maybe even one-year – increments.

Because small changes in age at menopause lead to differences in both risk and exposure, broad categories of age would mask these differences and would lead to biased estimates (Colditz, 1998). Fine stratification on age at menopause is therefore integral to the calculation of unbiased risk estimates. In the ECS data, there were too many unrepresented age groups to control for age at menopause as a continuous variable. Use of a continuous variable may not be necessary though; in the reanalysis of the data existing to date on HRT use and the risk of breast cancer, the Oxford researchers achieved full statistical control for age at menopause by creating five strata: <35, 35-39, 40-44, 45-49 and ≥50 (Collaborative Group, 1997). The categories set out by the Oxford investigators were therefore used in this analysis.
History of proliferative benign breast disease

Self-reported history of proliferative benign breast disease was used. Information on pathologic subtype was not available; therefore, no distinction could be made between proliferative disease with and without atypia.

Routine Mammograms

Information on mammograms was solicited in order to address a potential screening bias. It is possible that women on HRT are followed more carefully by their physicians and are more likely to receive mammograms. The questionnaire asked whether women had mammograms performed on a routine basis (every two years). Women who reported receiving routine mammograms based on a first mammogram performed following the appearance of symptoms of breast cancer or based on a second mammogram performed after diagnosis, were reclassified as not having routine mammograms. Although it was not known what prompted a woman to have her first mammogram, in order to ensure that only screening mammograms were included, only women whose first mammogram was at least two years before diagnosis were classified as having routine mammograms.

Age at first pregnancy

Age at first pregnancy was defined as the age of the woman at the end of her first pregnancy which lasted 5 months or more, regardless of the outcome of the pregnancy.
Parity

Parity was defined as the number of pregnancies resulting in live births, either single or multiple births. Multiple births counted as one towards parity.

Breast feeding

Number of months of breast feeding was assessed as the cumulative number of months breast feeding over all pregnancies.

Family history of breast cancer

The question posed was whether or not an immediate blood relative had ever been diagnosed with cancer. Respondents often listed aunts, uncles or grandparents who had cancer diagnoses, but only mothers, fathers, sisters, brothers, sons or daughters were considered. Two variables were created. one which reflected family diagnoses of breast cancer only and a second which included ovarian cancer as well. The number of first degree relatives with breast or ovarian cancer was also assessed.

Smoking variables

Respondents were asked to indicate whether they had smoked at least 100 cigarettes in their entire life. They were asked to indicate the age at which they started smoking, the number of years in total that they had smoked, and the average number of cigarettes smoked per day. They were also asked to indicate if they had quit smoking, and if so, at what age. Respondents could then be categorized into never, current, and former smokers (smoking status was censored at diagnosis date). Pack years were calculated according to the following
formula: pack years = (average # of cigarettes smoked per day x total years smoked) / 22.5 cigarettes per pack. While passive smoking may be associated with risk of breast cancer, it is unlikely associated with HRT use and, therefore, in this analysis no attempt was made to assess exposure to passive smoke.

**Body mass index (BMI)**

BMI equals weight (kg)/ height (m²). Categories were created according to previously defined biological thresholds (Diehr et al., 1998). Those with a BMI ≥ 30 were defined as obese. Normal weight (BMI=20.0-24.9) was used as the referent category. Max BMI is a reflection of the most a woman ever weighed (highest weight (kg)/ height (m²)), excluding pregnancy.

**Education**

Because of the variation in the length of high school, if the highest grade of high school or elementary school completed was either grade 12 or 13, then women were classified as having a high school education. If the highest grade was greater than or equal to 12 and the number of years of post-secondary education was greater than zero, but less than four then they were classified as having some post-secondary education. If four or more years of post-secondary school was completed, women were placed in the highest category of education. In many instances, categorization was not this simple and answers required interpretation. Some women for example indicated that the highest grade of school completed was well below 12 and then indicated a certain number of years of post-secondary education (which is possible if they considered trade school as post-secondary). If the combined number of years
recorded for school and college was less than 12, they were placed in the lowest level of education. If the combined number of years was equal to 12 or 13, they were classified as having completed high school; if it was 14-15, they were classified as having some post-secondary education; if it was greater than or equal to 16 they were classified as having four or more years of post-secondary education.

**Alcohol consumption**

For each of beer, wine and liquor, the number of drinks consumed per day was determined based on the values recorded in the dietary section of the ECS questionnaire. When a range was presented (i.e. 5-6 per week), the mid-point of the range was used (i.e. 5.5 drinks per week → 5.5/7 drinks per day). The alcohol content per average serving of beer, wine and liquor varies as does the number per serving. The number of grams of alcohol consumed per day was calculated according to the following formula:

<table>
<thead>
<tr>
<th></th>
<th>ml/average serving</th>
<th>g alcohol/ml</th>
<th>drinks/day</th>
<th>g of alcohol/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer</td>
<td>341</td>
<td>0.055</td>
<td>b</td>
<td>341<em>0.055</em>b</td>
</tr>
<tr>
<td>Wine</td>
<td>130</td>
<td>0.11</td>
<td>w</td>
<td>130<em>0.11</em>w</td>
</tr>
<tr>
<td>Liquor</td>
<td>50</td>
<td>0.4</td>
<td>l</td>
<td>50<em>0.4</em>l</td>
</tr>
</tbody>
</table>

Odds ratios based on number of drinks consumed per day are more easily interpretable than are risks in terms of the number of grams of alcohol consumed per day. Alcohol consumption, in terms of number of drinks consumed, was arrived at by dividing the total number of grams of alcohol consumed per day by 17.7, the average number of grams of alcohol in an alcoholic beverage (average of beer, wine and liquor).

Total number of drinks of alcohol consumed per day:

\[ = \frac{[(341\times0.055\times b) + (130\times0.11\times w) + (50\times0.4\times l)]}{17.7} \]
Fat consumption

Total fat intake was assessed based on the consumption of 26 food items included in the dietary history (question 19, appendix A). These 26 foods represent approximately 80% of one’s total fat intake (Cotterchio, 1999). The fat content in an average serving of each of these items was derived from a Health Canada publication entitled “Nutrient Value of Some Common Foods” (1998). As with alcohol, when a range in consumption was reported for foods, the midpoint was used. The number of servings consumed per day was multiplied by the number of grams of fat in each serving and summed across all 26 items to yield the total fat intake per day. Intake was then divided into quartiles based on the distribution among controls. The 26 food items along with their corresponding fat content are:

<table>
<thead>
<tr>
<th>Food item</th>
<th>Approximate fat content (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>whole milk (8 oz.)</td>
<td>9</td>
</tr>
<tr>
<td>2% milk</td>
<td>5</td>
</tr>
<tr>
<td>french fries/ fried potatoes (1/2 cup)</td>
<td>10</td>
</tr>
<tr>
<td>chicken/turkey (4 oz.)</td>
<td>7</td>
</tr>
<tr>
<td>beef, pork or lamb (4oz.)</td>
<td>15</td>
</tr>
<tr>
<td>hamburger (1)</td>
<td>17</td>
</tr>
<tr>
<td>hot dog (1)</td>
<td>10</td>
</tr>
<tr>
<td>salami, bologna (1 piece)</td>
<td>3</td>
</tr>
<tr>
<td>smoked meat or corned beef (1 piece)</td>
<td>5</td>
</tr>
<tr>
<td>bacon (1 slice)</td>
<td>3</td>
</tr>
<tr>
<td>sausage (1)</td>
<td>5</td>
</tr>
<tr>
<td>egg (1)</td>
<td>7</td>
</tr>
<tr>
<td>cheese (not cottage) (1 slice/1 oz.)</td>
<td>9</td>
</tr>
<tr>
<td>cake (1 slice)</td>
<td>9</td>
</tr>
<tr>
<td>cookies (1)</td>
<td>16</td>
</tr>
<tr>
<td>doughnuts, pastry (1)</td>
<td>3</td>
</tr>
<tr>
<td>pies (1 slice)</td>
<td>10</td>
</tr>
<tr>
<td>ice cream (1/2 cup)</td>
<td>7</td>
</tr>
<tr>
<td>chocolate (1 bar/1 oz.)</td>
<td>15</td>
</tr>
<tr>
<td>potato chips (small bag or 45 g)</td>
<td>8</td>
</tr>
<tr>
<td>peanut butter (1 tbsp.)</td>
<td>15</td>
</tr>
<tr>
<td>nuts (1 oz/30 g)</td>
<td>4</td>
</tr>
<tr>
<td>margarine on bread or vegetables (1 pat/tsp.)</td>
<td>4</td>
</tr>
<tr>
<td>butter on bread or vegetables (1 pat/tsp.)</td>
<td>7</td>
</tr>
<tr>
<td>mayonnaise or salad dressing (1 tbsp.)</td>
<td>11</td>
</tr>
</tbody>
</table>
3.2.3 Missing Values

The data entry system was set up such that the default value to the question: “have you ever taken hormone replacement medication for six months or more” was no. Thus, there were no missing values for the ever/never use. Current/former HRT use could not be assessed for 2% of cases and 1% of controls. Duration of HRT use could not be assessed for 8% of cases and 8% of controls.

No distinction was made between unknown and missing values. Any subject who had a missing or unknown value for a variable included in the model was excluded from that particular analysis – with exceptions. In computation of the total fat intake and the physical activity variables, an effort was made to impute missing values where it was reasonable to do so. The question regarding milk intake was repeated four times, once for each of whole, 2%, 1% and skim milk. Many people approached this as a grouped variable, only answering for one type of milk. If they had a missing value for any of the milk questions and did not specifically check ‘never...’ for any of the milk questions, it was assumed that consumption was never or less than 1 per month. There were some subjects who, throughout the entire dietary history, never once checked off the category ‘never or less than 1 per month’. It was assumed that these people (11 in total) were inclined to skip the question if they didn’t consume that particular food. For these subjects, the level of consumption was imputed as ‘never or less than 1 per month’ for any blank food item. In terms of physical activity, if a respondent filled in the activity level in their early 30’s but left the activity level for about 2 years ago blank and their age 2 years ago was between 31 and 34, then the value for their early 30’s was imputed and likewise for subjects in their early 50’s. Finally, the variable
'history of benign breast disease' was categorized as yes/quit/don't know and those who indicated "don't know" were included in the analysis.

3.3 Data Analysis

Odds ratio estimates and the associated 95% confidence intervals (CIs) were derived using unconditional logistic regression, fitted by the method of maximum likelihood. Established and suggested breast cancer risk factors were considered as potential confounders; if the p-value associated with the likelihood ratio statistic relating the variable to the risk of breast cancer was equal to 0.2 or less, then the effect of the variable on the main analyses was evaluated. These selected potential confounders were systematically entered in every analysis (timing of use, duration, latency) to determine if they were indeed confounders. If any of the odds ratio estimates for breast cancer changed by more than 10% upon the addition of the exposure variable of interest, that confounder was controlled for in all multivariate analyses. When more than one variable was identified as a confounder, the variables were entered into the model in alternating order to determine which, if not both, was mediating the effect. Because of the high degree of correlation between type of menopause, ovarian status and oophorectomy, these terms were never entered together in a model. For all comparisons, the reference category was composed of women who had never taken any type of hormone replacement therapy. Several variables were tested for interaction with long-term HRT use using nested hierarchical modeling.
Chapter 4
Results

4.1 Breast cancer risk factors

The post menopausal women included in this analysis consisted of 404 cases and 403 controls. Only those whose menopausal status could be determined were included. Cases were significantly more likely than controls to report a history of benign breast disease, to have a family history of breast cancer, to be obese, to be tall, to have four or more years of post-secondary education, to have been of older age at first pregnancy, to report an older age at menopause and to have had routine mammograms (Table 6). Women who had their first full-term pregnancy after age 24 had a 50% increased risk, relative to women whose first pregnancy was at age 24 or earlier (OR=1.5, 95% CI=1.1-2.0). Women who went through menopause after age 44 had about an 80% excess in risk, a level which persisted with further increases in age. Having routine mammograms was associated with risk (OR=1.4, 95% CI=1.0-1.8). Compared to women who attained an education up to grade 12, having 4 or more years post-secondary education was associated with an increase in risk (OR=1.7, 95% CI=1.1-2.7). Body build was also related to risk; obese women were at increase risk compared to women of "normal" body weight (OR=1.6, 95% CI=1.1-2.4) as were tall women (height ≥165 cm: OR=1.4, 95% CI=1.0-2.0). Cases were more likely to report a history of benign breast disease (OR=3.0, 95% CI=1.8-5.0). Positive family history of breast cancer was also a risk factor (OR=2.0, 95% CI=1.3-3.0). Although non-significant, there appeared to be a trend of increasing risk of breast cancer with higher fat intake. Contrary to the notion that physical activity may decrease risk of breast cancer, the data suggest that exercise may increase risk (particularly exercise at a young age).
Table 6. Odds ratios and 95% confidence intervals of breast cancer according to selected characteristics

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<tr>
<th>Variable</th>
<th>Cases (N=404)</th>
<th>Controls (N=403)</th>
<th>OR* (95% CI*)</th>
<th>LRS p value</th>
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Table 6 cont’d. Odds ratios and 95% confidence intervals of breast cancer according to selected characteristics

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Table 6 cont’d. Odds ratios and 95% confidence intervals of breast cancer according to selected characteristics

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<td>23.1</td>
<td>94</td>
<td>23.4</td>
</tr>
<tr>
<td>four or more years post-secondary</td>
<td>56</td>
<td>13.9</td>
<td>37</td>
<td>9.2</td>
</tr>
<tr>
<td>Married</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>never</td>
<td>19</td>
<td>4.7</td>
<td>20</td>
<td>5.0</td>
</tr>
<tr>
<td>ever</td>
<td>384</td>
<td>95.3</td>
<td>383</td>
<td>95.0</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>393</td>
<td>97.3</td>
<td>399</td>
<td>99.0</td>
</tr>
<tr>
<td>Jewish</td>
<td>11</td>
<td>2.7</td>
<td>4</td>
<td>1.0</td>
</tr>
<tr>
<td>Fat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1: &lt;26 g/day</td>
<td>69</td>
<td>21.2</td>
<td>74</td>
<td>23.3</td>
</tr>
<tr>
<td>Q2: 26-35 g/day</td>
<td>63</td>
<td>19.4</td>
<td>82</td>
<td>25.9</td>
</tr>
<tr>
<td>Q3: 36-48 g/day</td>
<td>88</td>
<td>27.1</td>
<td>83</td>
<td>26.2</td>
</tr>
<tr>
<td>Q4: &gt;=49 g/day</td>
<td>105</td>
<td>32.3</td>
<td>78</td>
<td>24.6</td>
</tr>
</tbody>
</table>
Table 6 cont’d. Odds ratios and 95% confidence intervals of breast cancer according to selected characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (N=404)</th>
<th>Controls (N=403)</th>
<th>OR(^a) (95% CI(^b))</th>
<th>LRS(^c) p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol Consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>never or less than 1 drink/month</td>
<td>176</td>
<td>180</td>
<td>48.0</td>
<td>1.0 (0.8-1.7)</td>
</tr>
<tr>
<td>up to one drink/week</td>
<td>81</td>
<td>70</td>
<td>18.7</td>
<td>1.2 (1.0-2.4)</td>
</tr>
<tr>
<td>&gt;1 drink/week - &lt;1/day</td>
<td>77</td>
<td>74</td>
<td>19.7</td>
<td>1.1 (0.7-1.5)</td>
</tr>
<tr>
<td>1 drink/day or more</td>
<td>48</td>
<td>51</td>
<td>13.6</td>
<td>1.0 (0.6-1.5)</td>
</tr>
<tr>
<td>Physical Activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate leisure physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in mid-teens</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 time/week</td>
<td>75</td>
<td>108</td>
<td>27.9</td>
<td>1.0 (0.8-2.2)</td>
</tr>
<tr>
<td>1-5 times/week</td>
<td>176</td>
<td>150</td>
<td>38.8</td>
<td>1.4 (1.0-1.9)</td>
</tr>
<tr>
<td>&gt;5 times/week</td>
<td>135</td>
<td>129</td>
<td>33.3</td>
<td>0.8 (0.5-1.2)</td>
</tr>
<tr>
<td>in early 30's</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 time/week</td>
<td>92</td>
<td>104</td>
<td>26.9</td>
<td>1.0 (0.7-1.5)</td>
</tr>
<tr>
<td>1-5 times/week</td>
<td>224</td>
<td>183</td>
<td>47.3</td>
<td>0.7 (0.4-1.0)</td>
</tr>
<tr>
<td>&gt;5 times/week</td>
<td>73</td>
<td>100</td>
<td>25.8</td>
<td>0.8 (0.5-1.2)</td>
</tr>
<tr>
<td>in early 50's</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 time/week</td>
<td>87</td>
<td>99</td>
<td>25.6</td>
<td>1.0 (0.7-1.5)</td>
</tr>
<tr>
<td>1-5 times/week</td>
<td>203</td>
<td>156</td>
<td>40.4</td>
<td>1.4 (1.0-1.9)</td>
</tr>
<tr>
<td>&gt;5 times/week</td>
<td>45</td>
<td>78</td>
<td>20.2</td>
<td>0.7 (0.4-1.0)</td>
</tr>
<tr>
<td>N/A(^d)</td>
<td>53</td>
<td>53</td>
<td>13.7</td>
<td>0.7 (0.4-1.0)</td>
</tr>
<tr>
<td>two years ago</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 time/week</td>
<td>107</td>
<td>107</td>
<td>28.2</td>
<td>1.0 (0.7-1.5)</td>
</tr>
<tr>
<td>1-5 times/week</td>
<td>218</td>
<td>176</td>
<td>46.4</td>
<td>1.2 (0.9-1.7)</td>
</tr>
<tr>
<td>&gt;5 times/week</td>
<td>66</td>
<td>96</td>
<td>25.3</td>
<td>0.7 (0.4-1.0)</td>
</tr>
<tr>
<td>Strenuous leisure physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in mid-teens</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 time/week</td>
<td>149</td>
<td>184</td>
<td>47.4</td>
<td>1.0 (0.7-1.5)</td>
</tr>
<tr>
<td>1-5 times/week</td>
<td>178</td>
<td>135</td>
<td>34.8</td>
<td>1.6 (1.2-2.2)</td>
</tr>
<tr>
<td>&gt;5 times/week</td>
<td>67</td>
<td>69</td>
<td>17.8</td>
<td>1.2 (0.8-1.8)</td>
</tr>
<tr>
<td>in early 30's</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 time/week</td>
<td>220</td>
<td>243</td>
<td>64.6</td>
<td>1.0 (0.7-1.5)</td>
</tr>
<tr>
<td>1-5 times/week</td>
<td>144</td>
<td>115</td>
<td>30.6</td>
<td>1.4 (1.0-1.9)</td>
</tr>
<tr>
<td>&gt;5 times/week</td>
<td>17</td>
<td>18</td>
<td>4.8</td>
<td>1.0 (0.5-2.1)</td>
</tr>
<tr>
<td>in early 50's</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 time/week</td>
<td>219</td>
<td>219</td>
<td>57.8</td>
<td>1.0 (0.7-1.5)</td>
</tr>
<tr>
<td>1-5 times/week</td>
<td>96</td>
<td>81</td>
<td>21.7</td>
<td>1.2 (0.8-1.7)</td>
</tr>
<tr>
<td>&gt;5 times/week</td>
<td>12</td>
<td>17</td>
<td>4.6</td>
<td>0.7 (0.3-1.5)</td>
</tr>
<tr>
<td>N/A(^d)</td>
<td>53</td>
<td>56</td>
<td>15.0</td>
<td>0.8 (0.5-1.5)</td>
</tr>
<tr>
<td>two years ago</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 time/week</td>
<td>265</td>
<td>240</td>
<td>65.6</td>
<td>1.0 (0.8-1.5)</td>
</tr>
<tr>
<td>1-5 times/week</td>
<td>90</td>
<td>106</td>
<td>29.0</td>
<td>0.8 (0.5-1.1)</td>
</tr>
<tr>
<td>&gt;5 times/week</td>
<td>15</td>
<td>20</td>
<td>5.5</td>
<td>0.7 (0.3-1.4)</td>
</tr>
</tbody>
</table>
Table 6 cont’d. Odds ratios and 95% confidence intervals of breast cancer according to selected characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (N=404)</th>
<th>Controls (N=403)</th>
<th>OR* (95% CI)*</th>
<th>LRSb p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Freqc</td>
<td>%</td>
<td>Freqc</td>
<td>%</td>
</tr>
<tr>
<td>Occupational physical activity</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>in early 20’s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sitting or light</td>
<td>233</td>
<td>59.7</td>
<td>192</td>
<td>49.7</td>
</tr>
<tr>
<td>moderate</td>
<td>115</td>
<td>29.5</td>
<td>134</td>
<td>34.7</td>
</tr>
<tr>
<td>strenuous</td>
<td>21</td>
<td>5.4</td>
<td>32</td>
<td>8.3</td>
</tr>
<tr>
<td>N/Aa</td>
<td>21</td>
<td>5.4</td>
<td>28</td>
<td>7.3</td>
</tr>
<tr>
<td>in early 30’s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sitting or light</td>
<td>186</td>
<td>47.7</td>
<td>150</td>
<td>39.2</td>
</tr>
<tr>
<td>moderate</td>
<td>166</td>
<td>42.6</td>
<td>190</td>
<td>49.6</td>
</tr>
<tr>
<td>strenuous</td>
<td>19</td>
<td>4.9</td>
<td>24</td>
<td>6.3</td>
</tr>
<tr>
<td>N/Ae</td>
<td>19</td>
<td>4.9</td>
<td>19</td>
<td>5.0</td>
</tr>
<tr>
<td>in early 50’s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sitting or light</td>
<td>194</td>
<td>50.5</td>
<td>165</td>
<td>42.9</td>
</tr>
<tr>
<td>moderate</td>
<td>105</td>
<td>27.3</td>
<td>114</td>
<td>29.6</td>
</tr>
<tr>
<td>strenuous</td>
<td>11</td>
<td>2.9</td>
<td>15</td>
<td>3.9</td>
</tr>
<tr>
<td>N/Ae</td>
<td>77</td>
<td>20.1</td>
<td>91</td>
<td>23.6</td>
</tr>
<tr>
<td>two years ago</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sitting or light</td>
<td>184</td>
<td>49.5</td>
<td>167</td>
<td>45.1</td>
</tr>
<tr>
<td>moderate</td>
<td>83</td>
<td>22.3</td>
<td>91</td>
<td>24.6</td>
</tr>
<tr>
<td>strenuous</td>
<td>4</td>
<td>1.1</td>
<td>13</td>
<td>3.5</td>
</tr>
<tr>
<td>N/Ae</td>
<td>101</td>
<td>27.2</td>
<td>99</td>
<td>26.8</td>
</tr>
</tbody>
</table>

* OR indicates odds ratio estimate; CI, confidence interval.

a Adjusted for age strata.
b Likelihood ratio statistic.
c Total numbers may vary because of missing values.
d N/A indicates not applicable; respondent had not yet reached her early 50’s

Controls were significantly more likely to be of high parity and to report having surgical menopause. The protective effect of increased parity was most pronounced among those with parity equal to four, relative to nulliparous women (OR=0.5, 95% CI=0.3-0.8). Relative to women who experienced a natural menopause, menopause brought upon by hysterectomy seemed to confer protection (OR=0.7, 95% CI=0.5-1.0) as did hysterectomy with bilateral oophorectomy (OR=0.6, 95% CI=0.4-1.0).
4.2 Confounders

Type of menopause (natural, hysterectomy, hysterectomy and bilateral oophorectomy), age at menopause (<35, 35-39, 40-44, 45-49 and ≥50), and history of benign breast disease (yes, no, don’t know), were the only variables to confound the relationship between HRT use and risk of breast. Although cases and controls were matched on age, age was also controlled for (<49, 50-59, 60-69, 70-74) in order to eliminate any potential residual confounding.

Each of the confounders was related to HRT use in a predictable manner (Table 7). Women whose menopause was due to hysterectomy and bilateral oophorectomy were more likely to ever use HRT compared to women who had a natural menopause (OR=6.65, 95% CI=3.96-11.2), as were women who had a hysterectomy alone (OR=2.05, 95% CI=1.42-2.96), albeit to a lesser extent. Among women who have ever used HRT, women whose menopause was brought on by a hysterectomy were much more likely to have used HRT for 10 years or more as opposed to less than 10 years (OR=7.56, 95% CI=4.34-13.2) as were women who underwent hysterectomy along with bilateral oophorectomy (OR=10.61, 95% CI=5.49-20.5).

Women who experienced a later age at menopause were less likely to ever take HRT (≥55: OR=0.39, 95% CI=0.18-0.86) and if they took HRT, they were much less likely to take it for long durations (≥55: OR=0.15, 95% CI=0-0.45). Those with a history of benign breast disease who took HRT were less likely to have done so for long durations (OR=0.59, 95% CI=0.93-2.85).
Table 7. Odds ratios and 95% confidence intervals relating patterns of HRT use with identified confounders

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds of ever vs. never use</th>
<th>Odds of &gt;=10 vs. 0.5-10 yrs of use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR*</td>
<td>95% CI*</td>
</tr>
<tr>
<td>Type of menopause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>natural</td>
<td>1.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hysterectomy</td>
<td>2.05</td>
<td>(1.42-2.96)</td>
</tr>
<tr>
<td>hysterectomy &amp; bilateral oophorectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at menopause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>1.00</td>
<td>0.01</td>
</tr>
<tr>
<td>35-39</td>
<td>0.95</td>
<td>(0.48-1.88)</td>
</tr>
<tr>
<td>40-44</td>
<td>0.51</td>
<td>(0.27-0.96)</td>
</tr>
<tr>
<td>50-54</td>
<td>0.40</td>
<td>(0.22-0.73)</td>
</tr>
<tr>
<td>&gt;=55</td>
<td>0.39</td>
<td>(0.18-0.86)</td>
</tr>
<tr>
<td>History of benign breast disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>1.00</td>
<td>0.38</td>
</tr>
<tr>
<td>yes</td>
<td>1.19</td>
<td>(0.72-1.99)</td>
</tr>
<tr>
<td>don't know</td>
<td>1.32</td>
<td>(0.87-2.01)</td>
</tr>
</tbody>
</table>

*OR indicates odds ratio; CI, confidence interval; LRS, likelihood ratio statistic.

4.3 Type of hormone used

Thirty-two point seven percent of women with breast cancer and 29.8% of control women reported ever using HRT. The breakdown by type of HRT varies by case/control status; among controls, 63.3% used ERT only, 27.5% used CRT only, 7.5% used both ERT and CRT, at different times and 1.7% used hormones of unknown type. Among cases, the distribution is 56.8%, 36.4%, 5.3% and 1.5%, respectively.

It is important to note that HRT use is simply an amalgamation of ERT use, CRT use, non-concomitant ERT plus CRT use, and use of hormones of unknown type. This risk associated with HRT use therefore represents a combination of the risk associated with ERT and the risk associated with CRT as well as the risk for the 16 women (7 cases, 9 controls) who used both
ERT and CRT, and the 4 women (2 cases, 2 controls) who used an unknown type of hormone medication. Before assessing any odds ratio estimate derived from HRT use, it is important to consider the odds ratio according to the variable of interest for ERT and CRT users separately. If the odds ratios differ enough to preclude combining these two categories and if these estimates are based on large enough numbers to ensure stability, then the overall HRT estimate should not be given too much credence.

4.4 Timing of use (ever/never, current/former, recency)

Overall, the risk of breast cancer was similar in women who had ever and never used HRT (OR=1.14, 95% CI=0.81-1.61) (Table 8). (Note: The estimates discussed herein are the multivariate-adjusted odds ratio estimates.) The odds ratio estimate did not differ significantly from 1.0, regardless of the type of hormone used. The risk associated with current use, among HRT users was 1.18 (95% CI=0.79-1.78). Once again the risk did not differ appreciably between women using ERT and those using CRT. So, the risk associated with both ever and current use tends to be a non-significant excess of under 20%. The risk among former users did not differ significantly from unity either, but the magnitude and direction of the point estimate varied by type of hormone. Former ERT users had a slightly decreased risk (OR=0.96, 95% CI=0.51-1.81), while former CRT users had an increased risk (OR=1.78, 95% CI=0.58-5.50), based on small numbers.

The effect of time since quitting is best evaluated by considering ERT and CRT separately (Table 8). Stratification by time since quitting ERT (<5 yrs, ≥5 yrs ago) created a dichotomy in the risk estimates; women who quit less than 5 years ago had a increase in risk, relative to
Table 8. Odds ratios and 95% confidence intervals of breast cancer according to type of hormone replacement therapy and timing of use

<table>
<thead>
<tr>
<th>Hormone Use</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>OR(^a) (95% CI)</th>
<th>OR(^b) (95% CI)</th>
<th>OR(^a) (95% CI)</th>
<th>OR(^b) (95% CI)</th>
<th>OR(^a) (95% CI)</th>
<th>OR(^b) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All HRT(^a) users</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never(^d)</td>
<td>272</td>
<td>283</td>
<td>1.00 (0.85-1.55)</td>
<td>1.14 (0.81-1.61)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>132</td>
<td>120</td>
<td>1.15 (0.84-1.73)</td>
<td>1.11 (0.79-1.78)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>86</td>
<td>75</td>
<td>1.21 (0.84-1.73)</td>
<td>1.18 (0.79-1.78)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>44</td>
<td>42</td>
<td>1.09 (0.69-1.72)</td>
<td>1.09 (0.65-1.83)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quit &lt;5 yrs ago</td>
<td>20</td>
<td>11</td>
<td>1.92 (0.90-4.09)</td>
<td>1.71 (0.76-3.87)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quit &gt;=5 yrs ago</td>
<td>18</td>
<td>25</td>
<td>0.74 (0.39-1.39)</td>
<td>0.77 (0.38-1.60)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)HRT indicates hormone replacement therapy; ERT, estrogen replacement therapy; CRT, combination (estrogen and progestin) replacement therapy; OR, odds ratio; CI, confidence interval.

\(^b\) Adjusted for age.

\(^c\) Adjusted for age, age at menopause, type of menopause, history of benign breast disease.

\(^d\) The referent category comprises never users of any type of hormone replacement therapy.

\(^\text{Total numbers may vary because of missing values. HRT use includes an additional 20 women not found in either the ERT or CRT category, 16 of whom used both ERT and CRT at different times and 4 of whom used hormones of unknown type.}^\text{\textit{Adjusted for age.}}}
non users, (OR=1.71, 95% CI=0.76-3.87), while quitting greater than or equal to 5 yrs ago led to a decrease in risk (OR=0.77, 95% CI=0.38-1.68). Both confidence intervals include one, so no conclusions can be drawn with certainty. Among CRT users, there was a decline in risk with increasing time since quitting, but it did not fall below zero, and again was based on small numbers.

4.5 Duration of use

After adjustment for confounders, there was a significant increase in risk with exposure to HRT of ten years or more (OR=1.84, 95% CI=1.07-3.17) (Table 9). When the effect of extended duration of hormone use was broken down by type of hormone, there was some variation in the results. For women reporting ERT use only, there was a non-significant increase in risk with ten or more years use (OR=1.76, 95% CI=0.94-3.30). Women who used CRT for ten years or more had a significantly elevated risk (OR=4.03, 95% CI=1.11-14.64), although this risk was based on only 12 exposed cases. There was no excess risk among those reporting shorter durations of hormone use, regardless of the preparation. To the contrary, among users of ERT only, use of hormones for 6 months to one year resulted in a significant protective effect (OR=0.31, 95% CI=0-0.99).

Table 10 was constructed in an effort to integrate the data from Tables 8 and 9. Increases in risk were observed among both long-term users (≥ 10 years) and among former users who quit <5 yrs ago, but it is possible that one risk factor is confounded by the other. Table 10 shows that the increase in risk among HRT users who quit less than 5 years ago relative to those who quit 5 or more years ago exists even after duration is controlled for. It is worth noting the consistency of
Table 9. Odds ratios and 95% confidence intervals of breast cancer according to duration of use of hormone replacement therapy

<table>
<thead>
<tr>
<th>Duration (yrs)</th>
<th>All HRT* users</th>
<th>ERT* users only</th>
<th>CRT* users only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>No. of controls</td>
<td>ORa* (95% CI)</td>
</tr>
<tr>
<td>Never</td>
<td>272</td>
<td>283</td>
<td>1.00 (1.00)</td>
</tr>
<tr>
<td>&lt;1</td>
<td>13</td>
<td>18</td>
<td>0.75 (0.36-1.56)</td>
</tr>
<tr>
<td>1 to 4</td>
<td>30</td>
<td>25</td>
<td>1.24 (0.70-2.18)</td>
</tr>
<tr>
<td>5 to 9</td>
<td>26</td>
<td>30</td>
<td>0.90 (0.52-1.57)</td>
</tr>
<tr>
<td>&gt;=10</td>
<td>52</td>
<td>37</td>
<td>1.47 (0.93-2.32)</td>
</tr>
</tbody>
</table>

*HRT indicates hormone replacement therapy; ERT, estrogen replacement therapy; CRT, combination (estrogen and progestin) replacement therapy; OR, odds ratio, CI, confidence interval.

a Adjusted for age.
b Adjusted for age, age at menopause, type of menopause, history of benign breast disease.
c Those who took hormones for an unknown duration were excluded.
d The referent category comprises never users of any type of hormone replacement therapy.
Table 10. Odds ratios and 95% confidence intervals of breast cancer according to recency of long-term and short-term hormone replacement therapy use

<table>
<thead>
<tr>
<th>Hormone Use</th>
<th>All HRT* users</th>
<th>ERT* users only</th>
<th>CRT* users only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>No. of controls</td>
<td>OR* (95% CI*)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>272</td>
<td>283</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;10 years total use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>47</td>
<td>46</td>
<td>1.07</td>
</tr>
<tr>
<td></td>
<td>(0.67-1.69)</td>
<td>(0.55-1.51)</td>
<td>(0.51-1.92)</td>
</tr>
<tr>
<td>Quit &lt;5 yrs ago</td>
<td>9</td>
<td>8</td>
<td>1.18</td>
</tr>
<tr>
<td></td>
<td>(0.44-3.11)</td>
<td>(0.32-2.77)</td>
<td>(0.30-3.75)</td>
</tr>
<tr>
<td>Quit &gt;=5 yrs ago</td>
<td>13</td>
<td>19</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>(0.34-1.47)</td>
<td>(0.34-1.78)</td>
<td>(0.22-1.30)</td>
</tr>
<tr>
<td>&gt;=10 years total use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>36</td>
<td>28</td>
<td>1.35</td>
</tr>
<tr>
<td></td>
<td>(0.80-2.28)</td>
<td>(0.94-3.25)</td>
<td>(0.69-2.24)</td>
</tr>
<tr>
<td>Quit &lt;5 yrs ago</td>
<td>11</td>
<td>3</td>
<td>3.84</td>
</tr>
<tr>
<td></td>
<td>(1.06-13.94)</td>
<td>(0.97-14.01)</td>
<td>(0.73-10.57)</td>
</tr>
<tr>
<td>Quit &gt;=5 yrs ago</td>
<td>5</td>
<td>6</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>(0.26-2.85)</td>
<td>(0.22-3.89)</td>
<td>(0.39-7.06)</td>
</tr>
</tbody>
</table>

*HRT indicates hormone replacement therapy; ERT, estrogen replacement therapy; CRT, combination (estrogen and progestin) replacement therapy; OR, odds ratio; CI, confidence interval.

a Adjusted for age.
b Adjusted for age, age at menopause, type of menopause, history of benign breast disease.
c Total numbers may vary because of missing values.
d The referent category comprises never users of any type of hormone replacement therapy.
e The odds ratio for recent users (current users plus those who quit <5 years ago) of HRT for >=10 years = 2.00 (95% CI=1.13-3.53); for recent users of ERT for >=10 years, the OR=1.70 (95% CI=0.89-3.24).
the patterns, even where the estimates are not significant. It is only among those with 10 or more years exposure that the value of the risk estimate is above 1.0. Both variables impact the risk estimates, but it is long-term use which mediates the excess risk of breast cancer. The excess risk associated with long-term use was confined to recent users (those who used HRT within the past 5 years) (OR=2.00, 95% CI=1.13-3.53).

4.6 Latency

There was no suggestion of a latent effect of HRT use (Table 11). The results are stratified by duration of hormone use in order to distinguish any latency effect from that of long-term use. Recall that the odds ratio estimate associated with ten or more years of HRT use was 1.84 (95% CI=1.07-3.17) (Table 9). Higher risks were not observed among long-term users with the greatest interval since first use (>14 yrs: OR=1.57, 95% CI=0.81-3.07). Among women with less than ten years of HRT use, the risk never approached the excess risk of 84% seen among long-term users, regardless of time since first use. For women with less than 10 years use who first took HRT greater than 14 years ago the odds ratio was 0.61 (95% CI=0.23-0.61). The fact that the risk estimate is below unity is probably a reflection of

<table>
<thead>
<tr>
<th>Time since first use</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>272</td>
<td>283</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;10 years total use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>33</td>
<td>28</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.51-1.71)</td>
</tr>
<tr>
<td>5-9</td>
<td>23</td>
<td>22</td>
<td>1.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.56-2.17)</td>
</tr>
<tr>
<td>10-14</td>
<td>4</td>
<td>7</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.18-2.36)</td>
</tr>
<tr>
<td>&gt;14</td>
<td>9</td>
<td>16</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.23-1.61)</td>
</tr>
<tr>
<td>&gt;=10 years total use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-14</td>
<td>21</td>
<td>12</td>
<td>2.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1.02-5.11)</td>
</tr>
<tr>
<td>&gt;14</td>
<td>31</td>
<td>25</td>
<td>1.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.81-3.07)</td>
</tr>
</tbody>
</table>

*HRT indicates hormone replacement therapy; OR, odds ratio; CI, confidence interval
* Adjusted for age, age at menopause, type of menopause, history of benign breast disease

Table 11. Latent effect of HRT use and risk of breast cancer
the fact that these women, on average, would have quit HRT more than five years ago, a situation which was seen to decrease risk. Nevertheless, even women who used HRT for less than ten years beginning 10-14 years ago were not at increased risk (OR=0.67, 95% CI=0.18-2.36).

4.7 Subgroup effects

The salient point thus far seems to be that women who took HRT for ten years or more were at a significantly increased risk of breast cancer. In order to identify subgroups of women for whom this increased risk may be heightened, the effect of long-term HRT use was analysed according to family history of breast cancer, age group, smoking status, number of pack-years smoked, BMI, alcohol consumption, ovarian status and type of menopause (Table 12). There is evidence from previous studies that each of these risk factors may modify risk, in a plausible fashion. History of benign breast disease (BBD) could not be evaluated as a potential modifier of the effect of HRT because there were no controls with both a positive history of BBD and ten or more years of HRT use, thereby causing non-convergence.

Although none of the interactions were significant, the “lack of a statistical interaction does not support or refute the existence of a biologic interaction” (Chen & Colditz, 1999). Furthermore, non-significance may sometimes be a consequence of the method of categorization of the subgroup. If a subgroup is not stratified according to the biological threshold, the interaction term, as a whole, might not be significant. Where biological thresholds are not established, and where the analysis is still exploratory, it is instructive to make comparisons between different categories of a subgroup, after accounting for the effect of long-term HRT use.
Table 12. Possible modifiers of the effect of long-term HRT+ use on the risk of breast cancer

<table>
<thead>
<tr>
<th>Subgroup Characteristics</th>
<th>All HRT* users</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>OR^a</th>
<th>95% CI^c</th>
<th>p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family History : HRT use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.62</td>
</tr>
<tr>
<td>Never</td>
<td>225</td>
<td>259</td>
<td>1.00</td>
<td>(1.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>43</td>
<td>33</td>
<td>1.89</td>
<td>(1.03-3.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47</td>
<td>24</td>
<td>2.44</td>
<td>(1.35-4.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>9</td>
<td>4</td>
<td>3.12</td>
<td>(0.83-12.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age Group^b : HRT use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>25-49</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>33</td>
<td>39</td>
<td>1.00</td>
<td>(0.55-2.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>2</td>
<td>3</td>
<td>0.96</td>
<td>(0.11-8.19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Never</td>
<td>60</td>
<td>61</td>
<td>0.87</td>
<td>(0.36-1.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>13</td>
<td>9</td>
<td>2.22</td>
<td>(0.42-9.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>111</td>
<td>125</td>
<td>0.71</td>
<td>(0.37-1.40)</td>
<td></td>
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</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>30</td>
<td>16</td>
<td>2.12</td>
<td>(0.88-5.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-74</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Never</td>
<td>68</td>
<td>58</td>
<td>1.00</td>
<td>(0.49-2.09)</td>
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<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>7</td>
<td>9</td>
<td>0.49</td>
<td>(0.14-1.77)</td>
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<tr>
<td>OC use : HRT use</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>0.85</td>
</tr>
<tr>
<td>Never</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>195</td>
<td>202</td>
<td>1.00</td>
<td>(0.95-4.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>32</td>
<td>20</td>
<td>1.97</td>
<td>(0.36-1.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Never</td>
<td>17</td>
<td>20</td>
<td>0.79</td>
<td>(0.45-5.20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>4</td>
<td>4</td>
<td>2.01</td>
<td>(0.42-9.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>23</td>
<td>34</td>
<td>1.06</td>
<td>(0.55-2.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>8</td>
<td>7</td>
<td>1.52</td>
<td>(0.45-5.20)</td>
<td></td>
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</tr>
<tr>
<td>&gt;=10</td>
<td>31</td>
<td>24</td>
<td>1.45</td>
<td>(0.74-2.84)</td>
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</tr>
<tr>
<td>Smoking status : HRT use</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>0.66</td>
</tr>
<tr>
<td>Never</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>141</td>
<td>159</td>
<td>1.00</td>
<td>(0.57-3.23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>16</td>
<td>17</td>
<td>1.35</td>
<td>(0.57-3.23)</td>
<td></td>
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</tr>
<tr>
<td>Current</td>
<td></td>
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</tr>
<tr>
<td>Never</td>
<td>86</td>
<td>85</td>
<td>1.25</td>
<td>(0.82-1.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>24</td>
<td>14</td>
<td>2.29</td>
<td>(0.99-5.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Never</td>
<td>45</td>
<td>39</td>
<td>1.33</td>
<td>(0.75-2.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>12</td>
<td>6</td>
<td>3.41</td>
<td>(1.14-10.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pack years : HRT use</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Non-smoker</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>141</td>
<td>159</td>
<td>1.00</td>
<td>(0.56-3.21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>16</td>
<td>17</td>
<td>1.35</td>
<td>(0.56-3.21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-10</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>44</td>
<td>42</td>
<td>1.41</td>
<td>(0.82-2.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>13</td>
<td>5</td>
<td>3.84</td>
<td>(1.21-12.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-26</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Never</td>
<td>35</td>
<td>38</td>
<td>1.21</td>
<td>(0.63-1.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>9</td>
<td>8</td>
<td>1.45</td>
<td>(0.48-4.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=27</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>51</td>
<td>72</td>
<td>1.41</td>
<td>(0.82-2.41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>14</td>
<td>7</td>
<td>3.31</td>
<td>(1.05-10.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 12 (cont'd). Possible modifiers of the effect of long-term HRT* use on the risk of breast cancer

<table>
<thead>
<tr>
<th>Subgroup Characteristics</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>OR(^d)</th>
<th>95% CI**</th>
<th>p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI : HRT use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-24.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>112</td>
<td>119</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>25</td>
<td>21</td>
<td>1.88</td>
<td>(0.88-4.02)</td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>16</td>
<td>18</td>
<td>1.41</td>
<td>(0.64-3.09)</td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>2</td>
<td>1</td>
<td>6.27</td>
<td>(0.51-76.3)</td>
<td></td>
</tr>
<tr>
<td>25.29.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>70</td>
<td>97</td>
<td>0.88</td>
<td>(0.56-1.40)</td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>21</td>
<td>11</td>
<td>2.21</td>
<td>(0.86-5.70)</td>
<td></td>
</tr>
<tr>
<td>&gt;=30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>72</td>
<td>47</td>
<td>1.65</td>
<td>(0.98-2.76)</td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>4</td>
<td>4</td>
<td>1.57</td>
<td>(0.31-7.83)</td>
<td></td>
</tr>
<tr>
<td><strong>Drinks of alcohol : HRT use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-&lt;1/month</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>128</td>
<td>128</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>16</td>
<td>16</td>
<td>1.43</td>
<td>(0.61-3.35)</td>
<td></td>
</tr>
<tr>
<td>up to 1/wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>52</td>
<td>43</td>
<td>1.57</td>
<td>(0.92-2.67)</td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>13</td>
<td>11</td>
<td>1.82</td>
<td>(0.71-4.71)</td>
<td></td>
</tr>
<tr>
<td>&gt;1/wk-&lt;1/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>45</td>
<td>55</td>
<td>1.02</td>
<td>(0.61-3.35)</td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>14</td>
<td>7</td>
<td>3.46</td>
<td>(1.20-10.0)</td>
<td></td>
</tr>
<tr>
<td>1/day or more</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>30</td>
<td>33</td>
<td>1.06</td>
<td>(0.57-1.96)</td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>6</td>
<td>2</td>
<td>2.12</td>
<td>(0.31-14.6)</td>
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</tr>
<tr>
<td><strong>Ovarian status : HRT use</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Removed-before meno</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Never</td>
<td>11</td>
<td>19</td>
<td>1.00</td>
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</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>10</td>
<td>13</td>
<td>1.83</td>
<td>(0.48-6.90)</td>
<td></td>
</tr>
<tr>
<td>Removed-after meno</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>7</td>
<td>7</td>
<td>0.82</td>
<td>(0.18-3.75)</td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>9</td>
<td>6</td>
<td>2.09</td>
<td>(0.47-9.28)</td>
<td></td>
</tr>
<tr>
<td>Intact - and inactive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>220</td>
<td>218</td>
<td>1.49</td>
<td>(0.56-3.98)</td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>33</td>
<td>17</td>
<td>3.09</td>
<td>(0.99-9.67)</td>
<td></td>
</tr>
<tr>
<td><strong>Type of menopause : HRT use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natural</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>203</td>
<td>187</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>16</td>
<td>7</td>
<td>2.02</td>
<td>(0.75-5.43)</td>
<td></td>
</tr>
<tr>
<td>Hysterectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>57</td>
<td>74</td>
<td>0.84</td>
<td>(0.47-1.52)</td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>26</td>
<td>17</td>
<td>1.47</td>
<td>(0.67-3.26)</td>
<td></td>
</tr>
<tr>
<td>hys. + bilat ooph</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>10</td>
<td>17</td>
<td>0.6</td>
<td>(0.22-1.60)</td>
<td></td>
</tr>
<tr>
<td>&gt;=10 yrs</td>
<td>10</td>
<td>13</td>
<td>1.11</td>
<td>(0.40-3.05)</td>
<td></td>
</tr>
</tbody>
</table>

* Users of HRT for at least 10 years.

* HRT, hormone replacement therapy; OR, odds ratio, CI, confidence interval

* Adjusted for age (where applicable), age at menopause, type of menopause (where applicable), history of benign breast disease (where applicable).

* Total numbers may vary because of missing values.

* Based on -2 log likelihood test for interaction

* Risk estimate comparisons can only be made after stratification by age group since the age distribution is not representative of the population (due to matching by age strata).
The relationship between age group and long-term HRT use is the most notable example. Although the interaction was not significant (p=0.07), it was of borderline significance. Among women aged 60-69, long-term users had almost a 300% increase in risk compared to non-users of the same age (based on values recorded in Table 12: \(2.12/0.71=2.99\)). Among women aged 25-49, long-term users were not at an increased risk of breast cancer (0.96/1.00=0.96). The interaction term reflects the relationship between these two variables once the main confounding effects of age group and long-term use have been removed. By stratifying on age, any residual confounding effect of age has been removed and by assessing the difference between these two stratified risk estimates, 0.96 and 2.99, the confounding effect of long-term use will be removed. It then becomes clear that any adverse effect exerted by long-term use is much more pronounced among women aged 60-69 compared to women aged 25-49. Conclusions are similar for women aged 50-59 compared to women 25-49, but are not similar for women aged 70-74 (possibly due to small numbers) which likely explains why the interaction term was not significant.

The harmful effect of long-term HRT increased somewhat among women who consumed more than one drink per week and among women with a positive family history. There was a weaker, if not non-existent, effect of long-term HRT use in obese women. Among obese women (BMI >30) the point estimate associated with long-term HRT use was below unity, whereas in all other categories of weight, it was above one. In addition, the harmful effect of long-term HRT use seemed to be attenuated somewhat among women who used oral contraceptives for more than ten years. There was no evidence of a meaningful interaction between hormone use and smoking status, pack-years smoked, ovarian status or type of menopause.
Chapter 5
Discussion

5.1 Interpretation of Results

The main finding is that the risk of breast cancer in postmenopausal women is significantly increased only after ten or more years of HRT use, to an excess risk of 84%. The direction of this association is consistent with the findings of four recent studies and, furthermore, the magnitude of the association falls within the range in risk reported by these four studies (range in RR's=1.43-2.43) (Yang et al., 1992; Colditz et al., 1995; Persson et al., 1997; Magnusson et al., 1999).

This excess risk associated with long-term HRT use is reduced, if not completely eliminated five years after HRT use is discontinued. The contribution of CRT to breast cancer risk among former, long-term users could not be addressed because this regimen has come into use only recently. These results are in concordance with studies that have stratified results by timing of ERT use and found an increased risk among current users relative to former users. (Colditz et al., 1992; Schairer et al., 1994). The transient increase in risk supports the finding that estrogen acts as a promoter of breast cancer, accelerating the growth of breast tumors that are already present.

The gradient in level of risk, in decreasing order, seems to go from women who quit less than five years ago to current users to women who quit five or more years ago. The fact that women who quit less than five years ago are at the highest risk of breast cancer is likely a reflection of the fact that this group includes women who ceased using HRT upon suspicions
or diagnosis of breast cancer. Due to the nature of the temporal relation, the effects seen among such women cannot be attributed to HRT.

No significant heterogeneity was found between odds ratio estimates of ERT versus CRT use. Nevertheless, somewhat higher point estimates were seen in CRT users, particular for 10 or more years of use. The point estimate associating long-term CRT use with a four-fold increased risk of breast cancer did reach significance but should not be given undue credence due to the lack of precision, the absence of a significant difference between ERT estimates and CRT estimates and the fact that the point estimate was much higher than estimates from other studies. Furthermore, the point estimate fell well outside of the confidence interval reported in 4 of 5 other studies (CI range of these 4 studies together =0.2-2.4) (Kaufman et al., 1991; Schairer et al., 1994; Newcomb et al., 1995; Stanford et al., 1995). Only two studies have reported significant estimates; Kaufman et al. (1991) associated 6 or more years of use of CRT with an increased risk (OR=1.6, 95% CI=1.1-2.1) and Schairer et al. (1999) found that the risk of breast cancer increased by 8% with each additional year of CRT use. It is thus prudent to interpret this finding cautiously by stating that the addition of progestin to the replacement regimen offered no protection. Still, the results do raise concern about the long-term use of CRT.

There is also a suggestion of a decreasing risk associated with use of HRT for less than one year. This finding is possibly confounded by the indications for short-term use and a sign of the internal hormonal milieu prior to taking HRT rather than a reflection of the ability of short-term use to confer protection.
The effect of long-term use was only apparent among women whose current age was over 50 years. Although not a significant interaction, this finding is consistent with data from several studies that suggested an increased risk associated with long-term use among older women, independent of the duration of hormone use (Colditz et al. 1995; Palmer et al., 1991; Collaborative Group, 1997). By virtue of the fact that the potential lifetime accumulation of damage to the DNA is greater in women who have lived longer, perhaps the breast cells of older women have already undergone some changes on the way to neoplasia and therefore respond differently than the normal breast cells of younger women to the presence of HRT. It is also possible that younger women have an inherent altered ability to metabolize or respond to hormone signals. Postmenopausal women under 50, on average, would have had a surgical menopause and it is possible that the indications for such surgery (i.e. endometriosis, reproductive cancers, ovarian cysts, fibroids, menstrual haemorrhaging, genital prolapse) (Naylor et al., 1994; Schairer et al., 1997) are the consequence of a disrupted hormonal system.

5.2 Limitations of the results

A causal relation between HRT and breast cancer is based partially on the existence of an association with both dose and duration – factors that could not be fully explored in this analysis. Presumably, the biologic threshold of immunity to HRT was surpassed with ten years of exposure. If the effect of HRT was further heightened with increasing duration past ten years, this would lend credibility to the putative causal relationship. Unfortunately, there were not enough women who used HRT (either ERT or CRT) for more than 15 years, thus exploration of a possible linear increase in risk past 10 years was not possible. Information
on the dose of estrogen or progestin was not solicited, so a dose-response relationship could not be evaluated.

Because the use of CRT has only recently become prevalent, the number of long-term CRT users (≥10 years) in this study were few (12 cases, 4 controls). While the odds of breast cancer among long-term CRT users was substantially greater than the odds associated with long-term ERT use, the confidence interval was quite wide (OR=4.03, 95% CI=1.11-14.64) and overlapped extensively with the confidence interval around the estimate for long-term ERT use (OR=1.76, 95% CI=0.94-3.30) (Table 9). The low numbers also hampered further stratification of CRT use by current/former use.

5.3 Methodological Issues

5.3.1 Validity of self-reported HRT use

Studies have found high agreement between self-reported HRT use and medication information derived from interview or prescription forms or physician records. By comparing questionnaire information with regard to duration of drug intake with information gathered from prescription forms (which were presently upon recruitment to the study), Persson et al. (1987) found the two sources to be highly correlated (correlation coefficient = 0.98). The validity of a single self-report question about postmenopausal estrogen use was assessed in the Postmenopausal Estrogen/Progestin Interventions Trial (PEPI) by comparing responses from a questionnaire to those obtained at interview. There was 95% agreement between estrogen use reported on the questionnaire and use derived from the interview (Greendale et al., 1997). Results from Goodman et al. (1990) indicate that women can recall estrogen use, (ever/never, duration and age at initiation) with a high degree of accuracy (answers were
verified by the physician). These results suggest that information solicited through a questionnaire can be adequately obtained.

5.3.2 Biases

*Measurement Bias*

Subjects may have been inaccurately classified on use of HRT. HRT use was censored at age of diagnosis. The questionnaire only allowed for reporting of an age, not a specific date. Anyone who started taking hormones at the same age as her age at diagnosis was classified as a non-user. To illustrate the problem that this introduced, consider the case of a woman diagnosed in December, 1998, at age 55 who started taking hormones in February 1998, also at age 55 (her month of birth is January). She would have been classified as a non-user even though she used hormones for 11 months before diagnosis. If recency of use is important then relevant exposure has been underestimated. Alternatively, HRT use could have been censored according to the year after diagnosis, but again misclassification ensues; some irrelevant exposure would be included and the misclassification would likely be differential (cases would likely cease taking HRT after a diagnosis of breast cancer), also, in this case some women who were taking hormones for less than six months before diagnosis would be classified as users. As it turns out, this involved very few women; only 6 ERT users (3 cases, 3 controls) and 6 CRT users (4 cases, 2 controls) started taking ERT/CRT at the same age they were diagnosed so the effect of the misclassification is minimal.

Pike et al. (1998) devoted an entire article specifically to address the bias involved in including women with simple hysterectomy (without bilateral oophorectomy) in studies
measuring the effects of HRT on breast cancer risk. Age at menopause potentially confounds the relationship between HRT and the risk of breast cancer; those with a younger age at menopause are more likely to use hormones and to use them for longer durations and the risk of breast cancer decreases with decreasing age at menopause. This latter association, however, may actually be mediated by declining exposure to ovarian hormones and not by age at menopause, per se. Age at menopause and age at ovarian cessation mean the same thing in all women except for those who have had a simple hysterectomy. In this analysis, women with simple hysterectomy were assigned an age at menopause equal to their age at hysterectomy. Assuming that age at hysterectomy is an underestimation of the true age at menopause (cessation of ovarian function), using this proxy measure and categorizing hysterectomized women along with those whose ovaries truly ceased functioning at a young age, effectively contaminates these younger “age at menopause” groups which leads to falsely increased risk estimates associating true age at menopause with breast cancer risk in the younger strata. Estimates of the effects of HRT will be biased toward the null because of the random error in the association between age at menopause and true age at menopause (Pike et al., 1998). An alternative approach adopted by Colditz et al. (1995) is to assign an age at menopause equal to the age when natural menopause has occurred in ≥ 90% of women – this too will lead to an underestimation in the estimate of the effect of HRT. A third option is to set the age at menopause at the age when a woman first used HRT and eliminate all those who never used HRT. but again, bias toward the null ensues (Pike et al., 1998). Short of excluding these women entirely, there is no satisfactory option. Ninety-eight cases and 112 controls attribute the onset of their menopause to simple hysterectomy – excluding them entirely from this analysis would have led to a large decrease in precision.
If hysterectomy advances the time of ovarian failure (due to damaged blood supplies to the ovaries) (Siddle et al., 1987) this would reduce the difference between age at menopause and age at true menopause, and the magnitude of this bias would decline. This notion is supported by Kreiger et al. (1999) who found a decreased risk of breast cancer associated with simple hysterectomy.

A sensitivity analysis which excluded all women with simple hysterectomy yielded an odds ratio associated with ten or more years of HRT use of 1.81 (95% CI=0.85-3.82). This estimate is not significantly different from the estimate that was arrived at when the entire sample was used (OR=1.81, 95% CI=1.07-3.17). The concern that this latter estimate reflects a spurious increase in precision around a biased point estimate was therefore unfounded.

**Classification Bias**

Inaccurate classification of subjects according to history of benign breast disease (BBD) is likely the largest source of bias in this study. Women who indicated that they did not know whether they had a history of BBD were placed in a separate category and were included in the analysis, with the knowledge that doing so would introduce a bias toward the null (Vach & Blettner, 1991). Proceeding in any other way would have necessitated making assumptions that could not be substantiated.

Instead of defining three categories, one option would have been to eliminate the "don’t know" group from the analysis. Because BBD was controlled for in the multivariate adjusted models, this would have resulted in a vast decrease in power (121 subjects; 99 cases, 22 controls indicated “don’t know” to this question and would have thus been excluded). Other
options included making extreme assumptions in reclassifying this group. It can be reasoned that the entire “don’t know” group should be categorized with those who had a negative history of BBD; confusion might have arisen among cases who know that they have breast cancer and are unsure as to whether BBD is tied in with or means the same thing as breast cancer, so they responded, “don’t know”. This is compatible with the inordinately high odds ratio estimate seen in this group (OR=6.6, 95% CI=4.0-10.8); what they have may not be BBD, but in fact breast cancer. Alternatively, one could argue that these women did indeed receive a diagnosis of BBD but that when they were subsequently diagnosed with breast cancer they were confused as to the results of their earlier biopsy; this too is compatible with the high risk estimate as BBD is a strong risk factor for breast cancer (London et al., 1992; McDivitt et al., 1992). Along these lines, they should be categorized with those who had a positive history of BBD.

Detection Bias

Information regarding routine mammograms was collected as an indicator of the level of surveillance. Seventy-two percent of long-term HRT users (>=10 years) had routine mammograms while only 53% of never users reported routine mammograms. More frequent mammographic examinations would lead to an earlier diagnosis of breast cancer. The 19% difference in mammographic screening rates is not large enough to account entirely for the 84% excess risk seen among long-term users. Furthermore, without knowing whether the excess cancers observed in this analysis among long-term users are due to an increased number of early stage, localized disease compared with advanced stage disease, it is impossible to attribute the increased risk, even in part, to better surveillance. In addition,
even though other studies have found an excess of more benign cancers, there is also evidence for increased mortality associated with estrogen use (Barrett-Connor, 1998) suggesting that an increased risk may be partially, but not wholly, explained by better surveillance and detection among HRT users.

There may be flaws inherent in using routine mammograms as a proxy for the level of surveillance. It is possible that women taking HRT are more likely to be screened but if they were diagnosed following their first mammogram, they would not have indicated that they received routine mammograms. So, although routine mammograms did not confound the relationship between HRT use and breast cancer risk, a diagnostic detection bias might still exist.

In theory, a more pronounced difference in level of surveillance could have been artificially suppressed because of the manner in which routine mammography was classified. Only women whose first mammogram was at least two years before diagnosis were classified as having routine mammograms. This was done to eliminate mammograms that were performed due to symptoms or suspicions of breast cancer. It is possible though that women who had mammograms within two years of diagnosis did so even in the absence of any symptoms of breast cancer and that HRT users in particular would have had mammograms during those two years. In reality, even when mammogram use was censored at diagnosis, 62% of non-users and 79% of users were screened and there was still no confounding (data not shown).

A second form of detection bias could have arisen by virtue of the fact that some physicians may choose to examine women for breast cancer and require a normal mammogram before
prescribing HRT (Barrett-Connor, 1998). HRT would be withheld from women with a positive mammogram; this is compatible with the finding that in the first five years after beginning HRT use there are not as many advanced stage breast cancers diagnosed as there are in subsequent years (Collaborative Group, 1997). Greater medical vigilance would lead to an underestimation of the effect of HRT on risk of breast cancer.

**Diagnostic suspicion bias**

The putative causal relationship between HRT and breast cancer risk has received widespread publicity. Physicians might be influenced by this knowledge, increasing the intensity of the diagnostic process. This is supported by the finding that women taking HRT tend to be diagnosed with early stage breast cancers (Barrett-Connor, 1998; Gapstur et al. 1999).

The impact of differential screening, if it exists, might be lessened because of a decreased sensitivity of screening mammography among women on estrogen replacement therapy (Laya et al., 1996) due to increased breast density (Boyd et al., 1998b).

**Bias due to confounding**

Most of the established risk factors were adjusted for in the multivariate models. Underlying levels of circulating estradiol levels, which are correlated with postmenopausal hormone use and risk of breast cancer (Collaborative Group, 1997), were not measured. In order to obtain an exact level of these hormones, blood samples would be necessary. There are certain variables, such as bone density and indications for HRT use, which are markers of the internal hormonal milieu. Failure to control for them might bias the results.
HRT use is advocated for the relief of menopausal symptoms such as hot flashes and mood swings. Women who report such physical symptoms have lower estrogen levels at menopause than women without symptoms (Erlik et al., 1982; Longcope et al., 1996) and are also more likely to take HRT (Johannes et al., 1994). This suggests that women who take postmenopausal hormones are, on average, at a lower risk of breast cancer at the time of menopause. Such confounding by indication would spuriously reduce the adverse HRT-breast cancer association, particularly when comparing hormone users with nonusers. The associations outlined above are unlikely to hold with long-term use.

While BMI was controlled for, bone density, which was not, might be a more precise marker of hormone levels. A strong association between high bone density and increased risk of breast cancer has been reported (Zhang et al., 1996). This is perhaps due to the fact that the level of circulating estradiol concentrations that decline with menopause decline to a more marked degree among postmenopausal women with a low bone mineral density (Cauley et al., 1996). In addition, bone density is lower in women when they begin taking postmenopausal hormones than in those who choose not to take them (Bauer, 1993). Together, this could lead to falsely low estimates of the effects of postmenopausal hormones.

**Bias due to residual confounding**

There is a great potential for confounding between the time since menopause and long-term use of HRT (Collaborative Group, 1997). Age at menopause was controlled for in this analysis by constructing five categories (one can control for time since menopause or equivalently, age at menopause along with current age). If the risk of breast cancer increases
progressively with both age at menopause and duration of use, it might be prudent to control for age at menopause as a continuous variable.

**Non-respondent bias**

Cases were more likely to respond than controls; the response rates were 86.5% for cases and 77.7% for controls. However, the overall response was high and there were no glaring differences in the frequency of non-response characteristics. Because these characteristics (i.e. general interest in study, too ill, questionnaire too personal, communication problems) are only marginally related to disease and not intuitively related to exposure, nonparticipants are highly unlikely to vary according to specific combinations of exposure and disease – the only scenario which would seriously affect study results (Kelsey et al., 1996).

If, however, one includes those who could not be located as non-respondents (in spite of the caveats outlined under ‘Response Rates’), a potential bias is revealed. When this group is included, the response rate among controls drops to 65.7% while the rate for the cases remains constant at 84.3%. Fifteen point five percent of cases and 2.6% of controls could not be located. If the controls who could not be located truly do relocate more often, for example, they might be less likely to have a regular family physician and less likely to be prescribed HRT or they might be less likely to develop cancer due to shorter exposure to unmeasured potential confounders such as environmental carcinogens. Without being able to account for every contingency, it is not clear what the overall effect of a non-respondent bias might be.
Ascertainment bias

Determination of the presence of breast cancer was not made in a uniform manner for cases and controls. Cases were identified through pathology reports submitted to the Ontario Cancer Registry, but the presence or absence of breast cancer in controls was not verified. Only those controls who were diagnosed during the period of ascertainment and were thus also identified as cases would have been excluded from the control group. Inclusion of controls who were, at any other time in their life, diagnosed with breast cancer, would lead to a bias toward the null. Given the low prevalence of breast cancer in the population, the results are likely not altered significantly due to this bias.

Selection bias

A potential source of bias is introduced by virtue of the fact that cases would have been filtered on selection criteria set by their physicians. The largest concern is that physicians may have declined consent to contact those patients who were acutely ill. The most aggressive types of cancers could, conceivably, be more likely to be associated with HRT use (although studies suggest otherwise). Referring to table 5, physicians refused to grant permission to contact only 3 breast cancer cases in the entire ECS study on the basis of their being too ill, not all of whom were necessarily even postmenopausal. Thus, the impact of this potential bias is negligible. Other reasons for physician refusal are: “not a good candidate” and “no reason given” – heterogeneous groups which are unlikely to be strongly related to HRT use in any one overwhelming direction. Selection bias is not a likely explanation for the observed associations.
Selection bias was minimized by selecting cases and controls from the same sampling frames (population of Ontario) as opposed to using hospital controls. Furthermore, high participation rates were obtained, again minimizing selection bias.

5.4 Implications of the results

Potential biases notwithstanding, it is unlikely that the association between long-term HRT use and breast cancer is spurious. If anything, bias would have led to systematic underestimation of the association. The results indicate that prophylactic therapies that can confer all of the benefits of HRT without leading to an increased risk of breast cancer are urgently needed.

Accordingly, studies examining the short and long-term effects of “designer estrogens” become the next logical focus. Designer estrogens are a class of drugs more accurately known as selective estrogen-receptor modulators (SERM’s). They are molecules designed to stimulate only α or β estrogen receptors, in only certain tissues, ideally functioning as an antiestrogen in the organs where too much estrogen is harmful (i.e. the breast and uterus), and as an estrogen mimic in organs where estrogen is beneficial (i.e. the heart and bones) (Franks & Steinberg, 1999). The result, then, would be a pill that diminishes menopausal symptoms and reduces the risk of heart disease and osteoporosis, simultaneously having no effect on the risk of breast cancer or, preferably, reducing it. The SERM’s now available do not meet this profile.

Tamoxifen and raloxifene are two examples of SERM’s. Tamoxifen has some of HRT’s cardiovascular properties although it does not reduce cardiac risk to the extent that HRT does
nor is it as effective as HRT at building bone (Yao & Jordan, 1998). Furthermore, it stimulates uterine cell growth (Yao & Jordan, 1998). In addition, tamoxifen is an estrogen antagonist, blocking the ability of natural estrogens to stimulate growth of breast tissue; one study reported a 45% reduction in the risk of breast cancer after 4 years of use among women at high risk (Josefson, 1998).

Raloxifene, the second designer estrogen developed, was marketed to help prevent osteoporosis, although it builds bone at only half the rate of HRT (Delmas et al., 1997). Like HRT and tamoxifen, it has some cardiovascular benefits but of the three, HRT is superior (Delmas et al. 1997; Walsh et al., 1998). Unlike tamoxifen and estrogen, raloxifene does not stimulate uterine cell growth (Delmas et al., 1997). It also lacks the deleterious association with breast cancer; a three year trial showed that raloxifene reduced the risk of breast cancer by 76% among women with osteoporosis (Cummings et al., 1999). Both tamoxifen and raloxifene triple a woman’s chances of developing blood clots in the legs and lungs and may even exacerbate some menopausal symptoms (Franks & Steinberg, 1999).

Ongoing research should lead to the development of more effective SERM’s. Until then, HRT may still be the best option for women who are at a high risk of cardiovascular disease. Brinton & Schairer (1997) lend perspective to the issue by noting that a white woman’s cumulative risk of death between the ages of 50 and 94 is estimated to be 31% from heart disease, 2.8% from breast cancer and 2.8% from hip fracture. The risk-benefit ratio for each of these hormone therapies should be evaluated and compared, bearing in mind each woman’s profile of risk.
References


Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52

Cotterchio, M. Antidepressant medication use and breast cancer risk, 1999.


Hsieh CC, Trichopoulos D, Katsouyanni K. Yuasa S. Age at menarche, age at menopause, height and obesity as risk factors for breast cancer: associations and interactions in an international case-control study. *Int J Cancer* 1990; 46(5): 796-800.


Pike MC, Ross RK, Spicer DV. Problems involved in including women with simple hysterectomy in epidemiologic studies measuring the effects of hormone replacement therapy on breast cancer risk. Am J Epidemiol 1998; 147(8): 718-21


Schliesman B, Robinson L. Serum estrogens: quantitative analysis of the concentration of estriol compared to estradiol and estrone. Meridian Valley Laboratory 1997.


Appendix A
Questionnaire
Guide to filling in this Questionnaire:

Please choose answers by marking a circle

- [ ] -

or printing in the boxes.

- [ ] - 94

- [ ] - April

This form asks a variety of questions about you and your environment, which may affect or be related to your health. The information you provide will help Canadians to understand more about preventing disease.

Please complete each question as best you can even if you are not sure of your answer.

You do not need to fill in the entire questionnaire all at once. You may wish to take a brief rest in the middle.

If you have any questions about the survey or would like help filling it out, please call

Ms. Bonnie James, Senior Project Manager

at (416) 217-1238 (you may call collect).

Please return this questionnaire within two weeks if possible. Thank you for your time.
**GENERAL INFORMATION**

1. Today's date
   - Month
   - Day
   - Year
2. Is anyone helping you (the person whose name appears on the covering letter) to complete this questionnaire?
   - No
   - Yes
   - Spouse
   - Other
   -- Please specify:

3. When were you born?
   - Month
   - Day
   - Year

4. Are you
   - Female
   - Male

5. To which **ethnic or cultural group(s)** did your ancestors belong?
   - French
   - Dutch
   - English
   - Jewish
   - German
   - Polish
   - Scottish
   - Black
   - Italian
   - Aboriginal
   - Irish
   - Métis
   - Ukrainian
   - Inuit
   - Chinese
   - Other
   -- Please specify:

   *Examples of other ethnic or cultural groups are: Portuguese, Greek, Indian, Pakistani, Vietnamese, Japanese, Lebanese, Haitian, etc.*

6. What is your **marital status**?
   - Single
   - Widowed
   - Married
   - Divorced/Separated
   - Common law
   - Other

7. What is the **highest grade** (or year) of high school or elementary school that you have completed?
   - Grade
   - Never attended school

8. How many years of **post-secondary** school have you completed?
   - Years
   - None

9. Have you smoked **at least 100 cigarettes** in your entire life?
   - No → Go to 10
   - Yes
   -- About how old were you when you **first started** smoking cigarettes?
   - Years
   -- About how many **years** in total did you smoke?
   - Years
   -- Of the entire time you smoked, how many cigarettes, on the average, did you smoke per day?
   - Per day
   -- Do you **smoke cigarettes now**?
   - No → How old were you when you **stopped** smoking?
   - Years
   - Yes → On the average, about how many cigarettes **a day** do you smoke now?
   - Per day

10. Have you ever smoked a **pipe or cigars** regularly?
    - No → Go to 11
    - Yes
    -- For how many years?
    - Years
    -- About how many pipes or cigars **per day**?
    - Per day

11. Have you ever used **chewing tobacco** regularly?
    - No → Go to 12
    - Yes
    -- For how many years?
    - Years
    -- About how many plugs **per day**?
    - Per day

12. How tall are you?
    - Feet
    - Inches or
    - Centimetres

13. How much did you **weigh** about 2 years ago?
    - Pounds or
    - Kilograms

14. What is the **most you have ever weighed**?
    - (Women should not include pregnancy.)
    - Pounds or
    - Kilograms
15. Please list each of the places in Canada you have lived for at least 1 year. Start with the most recent residence and follow back to your childhood. (If you cannot remember exact details, provide your best recollection, for example, nearest cross-street or intersection.) If you have lived outside Canada for at least 1 year, list only the years and country.

<table>
<thead>
<tr>
<th>TIME PERIOD</th>
<th>ADDRESS</th>
<th>TIME PERIOD</th>
<th>ADDRESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Year</td>
<td>Last Year</td>
<td>First Year</td>
<td>Last Year</td>
</tr>
<tr>
<td>1979 to 1981</td>
<td>97 Greargate Rd</td>
<td>1969 to 1971</td>
<td></td>
</tr>
</tbody>
</table>
EMPLOYMENT HISTORY
16. Please tell us about each job or occupation you had for at least 12 months both in Canada and elsewhere. Include seasonal work, part-time, etc., if you worked the equivalent of 12 months or more. Begin with your most recent job and continue back to your first job. Please estimate the time period if you cannot remember exact years. (Even if you have retired, we still require the information.)
If you have never been employed, check here □ and continue to Question 17.

<table>
<thead>
<tr>
<th>TIME PERIOD</th>
<th>Type of Industry, Business, or Service and Company Name</th>
<th>Main Job Duties</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Year</td>
<td>Last Year</td>
<td></td>
</tr>
<tr>
<td>Example:</td>
<td>19  to 19</td>
<td>Oil industry, Bluestar Oil Company</td>
</tr>
</tbody>
</table>

1  
2  
3  
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10
<table>
<thead>
<tr>
<th>ADDRESS</th>
<th>Main source of drinking water</th>
<th>Primary types of home heating (Mark those which apply.)</th>
<th>Were you aware of dusts or odours from industry while living at this residence?</th>
<th>How many regular smokers usually lived in this home with you?</th>
</tr>
</thead>
<tbody>
<tr>
<td>R7A 8A7</td>
<td>Town/city water&lt;br&gt;Dug well&lt;br&gt;Drilled well&lt;br&gt;Borehole&lt;br&gt;Other&lt;br&gt;Don't know</td>
<td>Oil&lt;br&gt;Natural gas/propane&lt;br&gt;Electric&lt;br&gt;Wood&lt;br&gt;Coal&lt;br&gt;Other&lt;br&gt;Don't know</td>
<td>Never or rarely&lt;br&gt;At least once a month&lt;br&gt;At least once a week&lt;br&gt;At least once a day</td>
<td>None 1 2 3 or more&lt;br&gt;Don't know</td>
</tr>
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<td>○ ○ ○ ○ ○ ○</td>
<td>○ ○ ○ ○ ○ ○</td>
<td>○ ○ ○ ○</td>
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<td>○ ○ ○ ○ ○ ○</td>
<td>○ ○ ○ ○</td>
<td>○ ○ ○ ○</td>
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<td>○ ○ ○ ○ ○ ○</td>
<td>○ ○ ○ ○ ○ ○</td>
<td>○ ○ ○ ○</td>
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<td>○ ○ ○ ○ ○ ○</td>
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<td>○ ○ ○ ○ ○ ○</td>
<td>○ ○ ○ ○ ○ ○</td>
<td>○ ○ ○ ○</td>
<td>○ ○ ○ ○</td>
</tr>
</tbody>
</table>
17. Have you ever worked with any of the following for more than one year?

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Don't know</th>
<th>At work</th>
<th>At home</th>
<th>How many years in total?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asbestos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arsenic salts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromium salts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadmium salts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coal tar, soot, pitch, creosote, asphalt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mineral, cutting or lubricating oil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzidine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Benzene</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isopropyl oil</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyestuffs</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinyl chloride</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pesticides</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Herbicides</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mustard gas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation sources</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Welding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wood dust</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

You are almost halfway through the questionnaire. This is a good place to take a short break, if you wish.

DIET INFORMATION

18. During the past 20 years have you ever taken any of the following vitamin or mineral supplements?

<table>
<thead>
<tr>
<th>Vitamin and Mineral type</th>
<th>How often?</th>
<th>For how many years in total?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes, but not regularly</td>
</tr>
<tr>
<td>Multiple vitamins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-carotene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-complex vitamins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selenium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Job Location(s)</td>
<td>Job Title</td>
<td>Status</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>City/town and province</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rocky Mountain House, Alberta</td>
<td>Gas plant operator</td>
<td>Full time</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
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<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>
19. This section asks about your eating habits about two years ago. Thinking back to that time, we ask you to mark the column that best describes how often, on average, you ate or drank the amount specified of each of the following foods and beverages. Please mark a response for each item.

<table>
<thead>
<tr>
<th>BEVERAGES MADE WITH WATER</th>
<th>Never or less than 1 per month</th>
<th>1-3 per month</th>
<th>1 per week</th>
<th>2-4 per week</th>
<th>5-6 per week</th>
<th>1 per day</th>
<th>2+ per day</th>
<th>4-5 per day</th>
<th>6+ per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffee (1 cup)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Tea (1 cup)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Orange or grapefruit juice from frozen concentrate (4 oz/115 ml glass)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Other juices or drinks from frozen concentrate (4 oz/115 ml glass)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Drinks from powdered drink crystals (4 oz/115 ml glass)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Tap water (8 oz/230 ml glass)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Bottled water (8 oz/230 ml glass)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OTHER BEVERAGES</th>
<th>Never or less than 1 per month</th>
<th>1-3 per month</th>
<th>1 per week</th>
<th>2-4 per week</th>
<th>5-6 per week</th>
<th>1 per day</th>
<th>2+ per day</th>
<th>4-5 per day</th>
<th>6+ per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole milk (8 oz/230 ml glass)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>2% milk (8 oz/230 ml glass)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>1% milk (8 oz/230 ml glass)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Skim milk (8 oz/230 ml glass)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Orange or grapefruit juice, fresh, bottled or canned (4 oz/115 ml glass)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Other juices or drinks, fresh, bottled or canned (4 oz/115 ml glass)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Tomato or vegetable juices (4 oz/115 ml glass)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Soft drinks (1 glass/bottle/can)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Beer (1 bottle/can)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Wine (1 glass)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Liquor (1 drink or shot)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

(continued)
19. (continued) Please mark the column that best describes how often, on average, you ate the amount specified of these foods **about two years ago**.

<table>
<thead>
<tr>
<th></th>
<th>Never or less than</th>
<th>1-3 per month</th>
<th>1-2 per week</th>
<th>2-4 per week</th>
<th>5-6 per week</th>
<th>1 per day</th>
<th>2-3 per day</th>
<th>4-5 per day</th>
<th>6+ per day</th>
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<tbody>
<tr>
<td><strong>FRUIT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apples or pears</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>(1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oranges (1)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Bananas (1)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Cantaloupe (¼ melon)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Other fruit, fresh or canned (1 piece or ½ cup)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td><strong>VEGETABLES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tomatoes (1 or ½ cup)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Carrots (1 whole or ¼ cup)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Broccoli (¼ cup)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Cabbage, cauliflower, brussels sprouts (½ cup)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Spinach or other greens (1 serving)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Yellow (winter) squash (½ cup)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Any other vegetable including green beans, corn and peas (½ cup)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Soups with vegetables (1 cup)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Potatoes: baked, boiled (1) or mashed (1 cup)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>French fries or fried potatoes (½ cup)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Sweet potatoes (1 or ½ cup)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Tofu or soybeans (3-4 oz/115 ml)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Baked beans or lentils (½ cup)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td><strong>BREADS AND CEREALS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bran or granola cereals, shredded wheat (1 cup)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Other cold cereals (1 cup)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Cooked cereals (1 cup)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>White bread (1 slice) or rolls (1)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Dark or whole grain bread (1 slice) or rolls (1)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Rice (1 cup)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Macaroni, spaghetti or noodles (1 cup)</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

(continued)
19. (continued) Please mark the column that best describes how often, on average, you ate the amount specified of these foods about two years ago.

<table>
<thead>
<tr>
<th>MEAT, POULTRY, FISH, EGGS &amp; CHEESE</th>
<th>Never or less than 1 per month</th>
<th>1-3 per month</th>
<th>1 per week</th>
<th>2-4 per week</th>
<th>5-6 per week</th>
<th>1 per day</th>
<th>2-3 per day</th>
<th>4-5 per day</th>
<th>6+ per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chicken or turkey (4 oz/115 ml)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Beef, pork or lamb as a main dish (steak, roast, ham) (4 oz/115 ml)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Beef, pork or lamb as a mixed dish (stew or casserole, pasta dish) (4 oz/115 ml)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Hamburger (1)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Hot dogs (1)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Luncheon meats (salami, bologna) (1 piece or slice)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Smoked meat or corned beef (1 piece or slice)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Bacon (1 slice)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Sausage (1)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Liver (4 oz/115 ml)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Fish, fresh, frozen or canned (4 oz/115 ml)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Fish, smoked, salted or dried (4 oz/115 ml)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Eggs (1)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Cheese other than cottage cheese (1 slice or 1 oz)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>SWEETS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cake (1 slice)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Cookies (1)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Doughnuts, pastry (1)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Pies (1 slice)</td>
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<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Ice cream (½ cup)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chocolate (1 small bar or 1 oz)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>MISCELLANEOUS</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potato chips (small bag or 45g)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Peanut butter (1 tbsp)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Nuts (1 oz/30g)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Margarine on bread or vegetables (1 pat or tsp)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Butter on bread or vegetables (1 pat or tsp)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Mayonnaise or salad dressing on bread or in salads (1 tbsp)</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
</tbody>
</table>
20. About two years ago:

<table>
<thead>
<tr>
<th>Question</th>
<th>Seldom or Never</th>
<th>Sometimes</th>
<th>Often or Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often did you <strong>add salt</strong> to your food?</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>How often did you <strong>add pepper</strong> to your food?</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>How often did you have <strong>onions or garlic</strong> in your food?</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>How often did you <strong>eat the skin on chicken</strong>?</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>How often did you <strong>eat the fat on meat</strong>?</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

21. What kinds of fat did you **usually use** in cooking about 2 years ago? Mark only 1 or 2.

- Block or stick margarine
- Soft tub margarine
- Low-calorie margarine
- Shortening
- Butter
- Oil
- Lard, bacon fat, fatback
- Non-stick spray or no fat
- Don't know or don't cook

22. What kinds of fat did you **usually put on** bread, potatoes and vegetables about 2 years ago? Mark only 1 or 2.

- Block or stick margarine
- Soft tub margarine
- Low-calorie margarine
- Butter
- Cream cheese
- Didn't add fat

23. Summary Questions

**About 2 years ago:**

<table>
<thead>
<tr>
<th>Question</th>
<th>Never or less than 1 per month</th>
<th>Less than 1 per week</th>
<th>1 to 2 per week</th>
<th>3 to 4 per week</th>
<th>5 to 6 per week</th>
<th>1 per day</th>
<th>1½ per day</th>
<th>2 per day</th>
<th>3 per day</th>
<th>4+ per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often did you use <strong>fat or oil in cooking</strong>?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Not counting salad or potatoes, <strong>how many servings of vegetables</strong> did you eat?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Not counting juices, <strong>how many servings of fruit</strong> did you eat?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>How often did you eat <strong>fried food</strong> from a restaurant or take-out? (for example, french fries, fried chicken, fried fish)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>
24. We have a few questions about your **usual eating habits 20 years ago**. What you have just told us about the different places you have lived and worked might help in remembering back to your eating habits at that time.

For each of the following foods and beverages, please indicate whether you **usually ate or drank more or less 20 years ago** than you did about 2 years ago. Please mark the appropriate column for each food or beverage.

<table>
<thead>
<tr>
<th>Compared to 2 years ago, 20 years ago I used to consume:</th>
<th>Much less</th>
<th>Somewhat less</th>
<th>About the same amount</th>
<th>Somewhat more</th>
<th>Much more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef, pork or lamb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chicken or fish</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bread</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Margarine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fried foods</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coffee</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft Drinks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
25. About 20 years ago:

<table>
<thead>
<tr>
<th></th>
<th>Never or less than 1 per month</th>
<th>Less than 1 per week</th>
<th>1 to 2 per week</th>
<th>3 to 4 per week</th>
<th>5 to 6 per week</th>
<th>1+ per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often did you eat steak</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>barbequed until charred or black?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>How often did you eat steak</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>broiled or pan fried until charred or black?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>How often did you eat hamburger</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>barbequed until charred or black?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>How often did you eat hamburger</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>broiled or pan fried until charred or black?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

26. Have you ever eaten fish caught in the Great Lakes, the St. Lawrence River, or rivers flowing into them?
- No — Go to 27
- Yes

About what year did you last eat fish caught in these waters? 19 [ ]

About what year did you first eat fish caught in these waters? 19 [ ]

About how many years have you been eating it? [ ] years

During those years, what was the usual number of meals you ate per year of fish from the Great Lakes, the St. Lawrence or rivers flowing into them?
- 1-10
- 11-20
- more than 20

27. Have you ever eaten wild duck or goose (from any location)?
- No — Go to 28
- Yes

About what year did you last eat wild duck or goose? 19 [ ]

About what year did you first eat wild duck or goose? 19 [ ]

About how many years have you been eating it? [ ] years

During those years, what was the usual number of meals of wild duck and goose you ate per year?
- 1-10
- 11-20
- more than 20

28. About how many times have you gone on a diet to lose weight during your adult life?
- Never
- 1 to 2 times
- 3 to 5 times
- 6 to 8 times
- 9 to 11 times
- 12 or more times
### PHYSICAL ACTIVITY

**29.** How often did you usually do strenuous physical activity or sports during the following time periods? (Some examples: racquet sports, hockey, basketball, soccer, jogging, aerobics, cycling, swimming, skiing or skating)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>In your mid-teens</th>
<th>In your early 30s</th>
<th>In your early 50s</th>
<th>About 2 years ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than once per month</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>1-3 times per month</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>1-2 times per week</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>3-5 times per week</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>More than 5 times per week</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Not applicable</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

**30.** How often did you usually do moderate physical activity or exercise for at least 20 minutes during the following time periods? (Some examples: brisk walking, gardening, yardwork, golf, bowling, curling, social dancing, softball, volleyball)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>In your mid-teens</th>
<th>In your early 30s</th>
<th>In your early 50s</th>
<th>About 2 years ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than once per month</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>1-3 times per month</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>1-2 times per week</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>3-5 times per week</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>More than 5 times per week</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Not applicable</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

**31.** What was your usual type of activity in your daily work, job or occupation (including homemaker, student, volunteer, etc.) during the following time periods?  
Please select the single best category for each age period.

<table>
<thead>
<tr>
<th>Type of Activity</th>
<th>In your early 20s</th>
<th>In your early 30s</th>
<th>In your early 50s</th>
<th>About 2 years ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting activity (e.g. desk job, telephone operator)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Light activity (e.g. driving, standing jobs)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Moderate physical activity (e.g. lifting and carrying light loads, heavy cleaning, carpentry)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Strenuous physical activity (e.g. carrying moderate to heavy loads, heavy construction or manual labour)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Not applicable</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>
### OTHER GENERAL INFORMATION

32. Before 2 years ago, did you ever feel depressed for at least 2 weeks?
   - No
   - Yes
   - Don't know

33. Before 2 years ago, were you ever diagnosed with clinical depression?
   - No
   - Yes
   - Don't know

34. Have you ever taken antidepressants for at least 2 weeks at any time in your life?
   - No → Go to 35
   - Yes
   - Don't know

Please check the antidepressants listed below that you have taken for at least two weeks at any point in your lifetime.

- Amitriptyline (Elavil)
- Desipramine (Norpramin)
- Doxepin (Tridapin)
- Maptroline (Luâiomil)
- Fluoxetine (Prozac)
- Nortriptyline (Aventyl)
- Paroxetine (Paxil)
- Trazodone (Desyrel)
- Imipramine (Tofianil)
- Clomipramine (Anafranil)
- PhenyZine (Nardil)
- Other -- Please specify:

For each of the antidepressants that you checked, how much did you take each day, and approximately when did you start and stop taking them? (If you have taken a drug more than once, please list each time period that you took the medication.)

<table>
<thead>
<tr>
<th>Name of antidepressant</th>
<th>Amount per day</th>
<th>Date started</th>
<th>Date stopped</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g. Doxepin</td>
<td>50 mg</td>
<td>Sept. 1961</td>
<td>Jan. 1964</td>
</tr>
</tbody>
</table>

35. When you were a child, did your mother smoke cigarettes in your presence?
   - regularly (every day or almost every day) as a heavy smoker
   - regularly (every day or almost every day) as a moderate smoker
   - regularly (every day or almost every day) as a light smoker
   - occasionally
   - never

36. When you were a child, did your father smoke cigarettes in your presence?
   - regularly (every day or almost every day) as a heavy smoker
   - regularly (every day or almost every day) as a moderate smoker
   - regularly (every day or almost every day) as a light smoker
   - occasionally
   - never

37. Has an immediate blood relative (mother, father, sister, brother) ever been diagnosed with cancer?
   - No → Go to 38
   - Yes

Please list the person's relationship to you and the type of cancer.

<table>
<thead>
<tr>
<th>Relationship to you</th>
<th>Type of cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g. father</td>
<td>lung</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
38. What was the approximate total income for all household members from all sources, before income taxes, in an average year during the last 5 years?

○ less than $10,000
○ $10,000 - $19,999
○ $20,000 - $29,999
○ $30,000 - $49,999
○ $50,000 - $99,999
○ greater than $100,000
○ prefer not to answer

39. How many members (adults and children) are there in your household in total?

[ ] persons

WOMEN:
Please continue to the next page.

MEN:
You have now completed the questionnaire.

Please take a moment to fill in any questions you may have missed.

THANK YOU VERY MUCH for taking the time to fill out this questionnaire. Your participation is sincerely appreciated.

Please return this completed questionnaire in the self-addressed envelope.
QUESTIONS FOR WOMEN ONLY

40. How old were you when you had your first menstrual period?
   [ ] years old
   ○ Don't remember
   ○ Haven't menstruated — Go to 44

41. Between the ages of 10 and 30, did your menstrual periods tend to occur regularly or irregularly (menstrual cycles varied by more than 10 days in length)? Please exclude any time when you were pregnant or using birth control pills.
   ○ Regularly
   ○ Irregularly

42. How old were you when you had your last menstrual period?
   [ ] years old
   ○ Still menstruate — Go to 44

43. How did your menstrual periods stop?
   ○ Naturally—that is, as part of the change of life
   ○ As a result of a hysterectomy (removal of womb)
   ○ Following radiation
   ○ Other — Please specify:

44. Have you had an operation to remove BOTH your ovaries?
   ○ No
   ○ Yes — At what age? If they were removed on two separate occasions, record when your second ovary was removed.
   At age [ ] years

45. Do you have mammograms (x-rays of the breast) performed on a routine basis (every two years)?
   ○ No
   ○ Yes — First mammogram at age [ ] years

46. Has a doctor ever diagnosed you as having proliferative benign breast disease?
   ○ No
   ○ Yes
   ○ Don't know

47. Have you ever used oral contraceptives for six months or more?
   ○ No — Go to 48
   ○ Yes
   Age first taken?
   [ ] years old
   Age last taken?
   [ ] years old
   Number of years used:
   before age 25 [ ] years
   age 25 and older [ ] years

48. Have you ever been pregnant?
   ○ No — Go to 54
   ○ Yes

49. How many times have you been pregnant? Include live births, stillbirths, miscarriages, abortions and ectopic (tubal) pregnancies.
   [ ] times

50. How old were you at the end of your first pregnancy?
   [ ] years old

51. How many of your pregnancies were live births?
   [ ] live births
   ○ none

52. How old were you at the end of your first pregnancy which lasted 5 months or more?
   [ ] years old

53. For how many months in total did you breastfeed? (Add the number of months that you breastfed after each birth to give the total number of months.)
   [ ] months
   ○ never breastfed
54. Have you ever taken **hormone replacement medication** for **six months** or more?

- [ ] No
- [ ] Yes

<table>
<thead>
<tr>
<th>What medication did you take?</th>
<th>Check all that apply</th>
<th>Age started</th>
<th>Age stopped</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen, oral or patch, alone (e.g. Premarin, Estroderm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen, oral or patch, and progesterone (e.g. Premarin and Provera)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progesterone alone (e.g. Provera)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other -- Please specify:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

*Please take a moment to fill in any questions you may have missed.*

**THANK YOU VERY MUCH** for taking the time to fill out this questionnaire. Your participation is sincerely appreciated.

*Please return this completed questionnaire in the self-addressed envelope.*