

**Review of the Literature of Risk Factors for Breast
Cancer in Adolescent and Young Adult Women
(15-39 years of age) &
Health Promotion Campaigns
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Introduction

Breast cancer is the fifth leading cause of cancer diagnosed in young Canadian women between 15 and 29 years of age, following thyroid, lymphomas, melanomas, and cervical cancers (Canadian Cancer Society, 2009a). Although breast cancer accounts for only about 5-8% of cancers diagnosed in women younger than 40 years of age, it is the leading cause of death from cancers for them (Leclère et al., 2013). Breast cancer is not a single disease. It is classified as ductal (within breast ducts), lobular (within the lobes of the breast), *in situ* (within the walls of the ducts or lobes), or invasive (extending beyond duct/lobe walls). There are four main subtypes of breast cancer with differing tumour characteristics including hormone receptor status (estrogen receptor (ER) and progesterone receptor (PR) positive or negative) and expression status of the human epidermal growth factor receptor-2 (HER2) gene. The molecular subtypes include: luminal A, luminal B, HER2 enriched, and triple negative (ER-, PR-, and HER2-negative) (Kohler et al., 2015). These subtypes have different risk factors, diagnostic descriptions, treatment options, and prognoses (Keegan, DeRouen, Press, Kurian, & Clarke, 2012). Further to this, some people have mutations to genes that produce tumour-suppressing proteins. Mutations in two such genes, the breast cancer gene 1 and 2 (BRCA1 and BRCA2) may be inherited and increase a person's risk of developing breast cancer, as do the TP53, CHEK2, PTEN, and other rare mutations.

Women diagnosed with breast cancer when they are younger than 40 years of age are more likely to have larger tumours at diagnosis ($\geq 2\text{cm}$), to be lymph node negative, estrogen receptor negative, be of a higher grade, less differentiated (stage II or higher), invasive, ductal, human epidermal growth factor receptor 2 positive, and are less likely to be a secondary cancer than women 40 years and older. On average, they also have a worse prognosis, with a lower percentage of young women expected to survive for five or more years after diagnosis than women diagnosed after the age of 40 years (Brinton, Sherman, Carreon, & Anderson, 2008; Dobi et al., 2011; Figueirdeu et al., 2007; Keegan et al., 2012; Maggard et al., 2003; Narod, 2012). The poorer prognosis for younger women may be due to differences in the underlying physiology of the disease making it less responsive to treatments formulated for and tested on older women (Ademuyiwa et al., 2015; Jmor et al., 2002; Maggard et al., 2003) and delayed diagnosis. These delays may be due to a combination of physician misdiagnosis and patient delays in seeking medical attention (Maggard et al., 2003; Simmons, Jayasinghe, Wold, & Melton, 2011). As such, the need to inform the general public, with a special emphasis on young women, and healthcare practitioners about the incidence and risk factors associated with early onset breast cancer may help reduce the burden of this disease in young women.

The goal of this review is to collate, assess, and synthesize the currently available literature of a) the incidence and risk factors for breast cancers in women 39 years of age or younger; b) to review and synthesize information on promotional programs to increase awareness and knowledge of the general public and/or healthcare providers regarding the incidence of and risk factors for breast cancers in younger women, and promotional programs to increase awareness and skills for self-detection of symptoms of breast cancers in young women.



Incidence of breast cancer

The incidence (number of people diagnosed per population) of breast cancers in women of all ages has been stable at about 100 cases per 100,000 women per year since 1990; about 25,000 cases per year in Canada (Canadian Cancer Society, 2015a). Similarly, the overall rate of breast cancer incidence has been stable in the USA for the past 10 years (Kohler et al., 2015). According to statistics gathered between 1996 and 2005 in Canada, there was a non-significant increase of 1.9% per year in the rate of breast cancer being diagnosed in women 15-29 years of age (Canadian Cancer Society, 2009a). In the USA, no change in the incidence has been reported for women younger than 40 years of age over the past decade (Anders, Johnson, Litton, Phillips, & Bleyer, 2009; Greenup et al., 2014; Hou & Huo, 2013; National Cancer Institute, 2006).

The incidence of breast cancer increases rapidly with age. The Public Health Agency of Canada estimates that in 2015, 95-125 cases of breast cancer will be diagnosed in women 15-29 years of age (31.5 per million) with another 1,050 cases in women 30-39 years old, 3,300 cases in women 40-49 years old, and 20,600 cases in women 50 years and older (Canadian Cancer Society, 2015a). A report from the USA indicates that the incidence of breast cancer is similar to that in Canada at 31.4 per million women 15-29 years old (National Cancer Institute, 2006) with a total of about 11,000 cases per year for women younger than 40 years of age (Miller, 2011).

Mortality from breast cancer

The overall mortality rate for breast cancer (the rate of death in people diagnosed) has been decreasing by about 1.6% per year since 1999 which is attributed to earlier and more sensitive tests of detection and improved therapies following diagnosis. The age-standardized mortality ratio was 23 per 100,000 in 2005 (Canadian Cancer Society, 2009a) compared with 20 per 100,000 in 2012 (Canadian Cancer Society, 2015a). However, although the five-year survival for 15-29 year old females improved from 69% to 73% between 1992-95 to 2001-04, the change was not significant indicating little or no improvement has occurred for young women (Canadian Cancer Society, 2009a). Of concern, the survival of young women with breast cancer is lower than the 80% five-year survival estimates for women of all ages (Canadian Cancer Society, 2015a). In the USA, the estimated five-year survival rate was higher for adolescents 15-19 years old at diagnosis (80%) and then dropped to 70-73% for women 20-34 years old before rising again to 78% for women 35-39 years old at diagnosis. Also, five-year survival rates are significantly lower for young women diagnosed with inflammatory breast cancer (20-30%) compared with other types of breast cancers: ductal, lobular, and medullary (National Cancer Institute, 2006).

About 5,000 Canadian women will die from breast cancer in 2015 (18 per 100,000), including 5-8 women aged 15-29 years (4% of those diagnosed), 100 (10% of diagnosed) women 30-39 years old, 360 (11%) women 40-49 years old, and 4550 (22%) in women 50 years and older (Canadian Cancer Society, 2015a). In a 2009 report focusing on cancers in adolescents and young adults 15-29 years old, it was estimated that breast cancer causes about 5.5 deaths per million young women, the highest mortality ratio for all cancers in this age group, causing 1041 potential years of life lost (Canadian Cancer Society, 2009a).



Risk & Protective Factors for Breast Cancer in Younger Women

Factors that are associated with breast cancer, either positively (higher/longer exposure is linked with breast cancer) or negatively (higher/longer exposure is protective against breast cancer), are different for women who are diagnosed before the age of 40 years compared to those diagnosed later in life (Althuis et al., 2003; Anders et al., 2009; Velentgas & Daling, 1994). Risk factors for women in general (most research is conducted with women who 40 years or older at diagnosis) include a personal or family history of cancer, Ashkenazi Jewish or African ancestry, age (55 years or older), early menarche (11-12 years or younger), late menopause (55 years or older), first pregnancy at 30 years or older or never pregnant, exposure to radiation, use of hormone replacement therapy, use of oral contraceptives, alcohol use, dense breasts or atypical hyperplasia of breasts, genetic conditions (ataxia-telangiectasia; Li Fraumeni, Cowden, & Peutz-Jeghers syndromes; CHEK2, BRCA1, & BRCA2 gene mutations), higher socioeconomic status, obesity, and being tall as an adult. Many factors that *may be* associated with a higher risk of breast cancer have been postulated but the available evidence is weak. More research is required before determining if diet, physical inactivity, smoking, stress, birth weight, exposure to diethylstilbestrol (DES), and some benign breast conditions are associated with an increased risk of breast cancer. Meanwhile, having a greater number of children and breastfeeding are considered protective against developing breast cancer (Canadian Cancer Society, 2015b; Cancer Care Ontario, 2013; Centers for Disease Control and Prevention, 2014; Public Health Agency of Canada, 2009). Even though not all of these risk factors are associated with breast cancer in young women, adopting a healthy lifestyle as early as possible may lower the odds of breast cancer developing. The following section reviews several potential risk and protective factors in populations of women younger than 40 years of age.

Oral contraceptive use

Several studies have attempted to assess the impact of using oral contraceptives on the risk of developing breast cancer. Most studies compared the ratio of people developing breast cancer in non-users (defined as those who either never used oral contraceptives or had used them for less than 12 months) compared to users (women who had use them for 12 months or longer) in a retrospective design, comparing women with and without breast cancer.

Six studies found a small positive, but not statistically significant, association with oral contraceptive use being a risk factor for breast cancer (Bethea et al., 2015; Chilvers et al., 1989; Haile et al., 2006; Jernström, Loman, Johannsson, Borg, & Olsson, 2005; McCredie, Dite, Giles, & Hopper, 1998; Tavani et al., 1999) while four studies (Brinton et al., 1995; Narod et al., 2002; Rosenberg et al., 1996; Wingo et al., 1991) reported a significant positive association with 1.4-1.7 times higher odds for users of oral contraceptives compared to non-users. Authors of one study reported that the use of oral contraceptives had no association with breast cancer incidence (Hennekens et al., 1984) while authors of another reported a negative association between oral contraceptive use and the odds of being diagnosed with breast cancer (Ursin et al., 1998). Two publications reanalyzed data from a previous study (Brinton et al., 1995); the first reported a positive association with estrogen-receptor negative (Althuis et al., 2003) while the second reported a positive association with triple-negative (Dolle et al., 2009) breast cancer but small, non-significant associations with non-negative receptor types of breast cancers for women using oral contraceptives.



Five of thirteen studies showed positive and statistically significant trends in *duration* of oral contraceptive use and early onset breast cancer (Brinton et al., 1995; Chilvers et al., 1989; Mayberry, 1994; McCredie et al., 1998; Pike, Henderson, Casagrande, Rosario, & Gray, 1981) and two showed a positive but not statistically significant association (Bethea et al., 2015; Rosenberg et al., 1996). Six showed no association between the length of use and the odds of breast cancer (Haile et al., 2006; Hennekens et al., 1984; Rookus & Van Leeuwen, 1994; Tavani et al., 1999; Tryggvadottir, Tulinius, Eyfjord, & Sigurvinsson, 2002; Ursin et al., 1998). In comparison to women who used oral contraceptives for less than one year (or never), the odds of breast cancer was 0.77-1.55 times that of women who used for 1 to 4-5 years, 1.0-1.8 times higher for women who used for 4-5 to 8-10 years, and 1.1-2.8 times higher for those who used oral contraceptives for at least 8-10 years.

Two studies reported that the odds of being diagnosed with breast cancer were 1.4-2.1 times higher for women who started using oral contraceptives before 20 years of age (Jernström et al., 2005; Rookus & Van Leeuwen, 1994) while in another study the odds of being diagnosed with breast cancer was 2.3 times higher for women who started using oral contraceptives before they were 18 years old compared to non-users and women who had used them for less than one year (Dolle et al., 2009). Five studies had positive, but not statistically significant, associations between using oral contraceptives before 18 or 20 years of age and being diagnosed with breast cancer (Chilvers et al., 1989; Haile et al., 2006; McCredie et al., 1998; Tavani et al., 1999; Wingo et al., 1991). Two studies reported no association between age of starting oral contraceptive use and breast cancer (Rosenberg et al., 1996; Ursin et al., 1998).

Of eight studies that compared whether there was an association between breast cancer diagnosis and how recently the women had used oral contraceptives, two showed a significant trend for decreased risk over time, with the odds of breast cancer dropping to that of non-users after ten years of non-use (Bethea et al., 2015; Haile et al., 2006) and five showed a non-significant decrease in risk 10-15 years after stopping (Dolle et al., 2009; McCredie et al., 1998; Rosenberg et al., 1996; Tavani et al., 1999; Wingo et al., 1991). One study showed no association between duration between stopping oral contraceptive use and breast cancer in young women (Ursin et al., 1998).

Researchers question whether the higher estrogen content ($\geq 50\mu\text{g}$) oral contraceptives, which were used until the 1970s in many countries, may be responsible for some of the increased risk for breast cancer in these early studies. One group of researchers reported no association between the estrogen content of the oral contraceptives and the risk of breast cancer in their participants (Ursin et al., 1998). Although authors of a second study reported slightly higher odds of breast cancer in women who used higher estrogen oral contraceptives, authors did not adjust for the age of the participants, which would confound the association since older women are at higher risk than younger women (Chilvers et al., 1989).

Biological variables

As noted earlier in this report, the incidence of breast cancer increases significantly with age. The Public Health Agency of Canada estimates that breast cancer is diagnosed in 4.7 per million 15-19 year olds, 55 per million 20-29 year olds, and 474 per million 30-39 year old Canadian women (Canadian Cancer Society, 2015a).



Younger women with a history of benign breast disease had 1.1-2.3 times higher odds of being diagnosed with breast cancer compared with women without a history. Although only four of the eight reviewed studies reported a statistically significant association between a history of benign breast disease and breast cancer, all of the studies reported a positive association, i.e., a higher odds of breast cancer for those with a history than those without (Althuis et al., 2003; Chilvers et al., 1989; Hill, Preston-Martin, Ross, & Bernstein, 2002; Mayberry, 1994; McCredie et al., 1998; Pike et al., 1981; Tavani et al., 1999; Wingo et al., 1991). It is possible that, for some young women, a previous diagnosis with benign breast disease may be a misdiagnosed case of breast cancer rather than a true risk factor for cancer (Jmor et al., 2002).

Several studies reported that being younger at menarche (first menstrual cycle) was associated with higher odds of developing breast cancer before the age of 40 years, with eight of the twelve reporting statistically significant associations. For women who experience menarche early in their adolescence (11 or 12 years or younger), the odds of developing early onset breast cancer are 1.05-1.2 higher per year compared with women who experience their first menstrual cycle later in their adolescence (15 years or older). Eight of the twelve reviewed studies found a statistically significant difference by age (Chilvers et al., 1989; Clavel-Chapelon et al., 1995; Jernström et al., 2005; Pike et al., 1981; Tavani et al., 1999; Tryggvadottir et al., 2002; Warner et al., 2013; Wingo et al., 1991), and another four studies reporting a non-significant association that matched the positive trend of the other studies (Althuis et al., 2003; Mayberry, 1994; McCredie et al., 1998; Negri et al., 1988).

The odds of women of African ancestry being diagnosed with early onset breast cancer are 1.6-2.7 times higher than the odds for Caucasian women while the risk for women of Asian, Hispanic, or other ancestry is unclear (Althuis et al., 2003; Innes, Byers, & Schymura, 2000). Surveillance data from the USA, from 1992-2004, indicated that African American women younger than 30 years of age had a 1.5 times higher risk while those 30-39 years old had a 1.08 times higher risk of being diagnosed with breast cancer than Caucasian women while Hispanic Americans had lower risks of being diagnosed than white or African Americans (Brinton et al., 2008). These estimates have *not* been adjusted for age at menarche or other potential risk factors.

Information on the impact of birth characteristics on the risk of developing breast cancer later in life is limited and often contradictory. Three of the four studies found no association between the odds of being diagnosed with breast cancer by the woman's weight at birth (Troisi et al., 2013; Troisi et al., 2006; Weiss-Salz et al., 2007) while one study reported that the odds of being diagnosed with breast cancer were 3.3 times higher for women born weighing more than 4500 grams than those weighing less (Innes et al., 2000). This study was the only one to categorize the top weight as 4500 grams or heavier, all others in the review used birth weights of 4000 grams or heavier as the highest category, which may have affected their estimates. No conclusions should be drawn from the results of one study without collaboration from other research.

In three studies of birth rank, authors of one study reported that the odds of a woman diagnosed with breast cancer being first-born were 1.3 times higher than if she was second- or third-born however, there was no association for other birth ranks (i.e., being born fourth or later) (Innes et al., 2000).



Furthermore, neither of the other two studies found any association between breast cancer incidence and birth order (Troisi et al., 2013; Weiss-Salz et al., 2007). Of note, each study used its own definition of the reference category (e.g., first-born versus later-born) making it difficult to determine if there were consistent trends across the studies. Also, due to declining numbers of women with three or more siblings, the data are based on small numbers and estimates are less reliable.

Body Size

Authors of one study reported that the odds of being diagnosed with breast cancer were 1.6-1.8 times higher for Australian women 165 cm (5'5") or taller compared with women who were shorter than 157 cm (5'2") as an adult (McCredie et al., 1998). On the other hand, a study of Icelandic women found no association between adult height and the odds of breast cancer (Tryggvadottir et al., 2002). No conclusive association is evident.

No studies found an association between adult weight and the risk of developing breast cancer in younger women (Chilvers et al., 1989; McCredie et al., 1998; Tryggvadottir et al., 2002). The results for body mass index (weight (kg)/height (cm) squared) are mixed. Authors of one study report a significant increase in risk for breast cancer with higher adult body mass indices (Mayberry, 1994) while authors for another study report no association (McCredie et al., 1998) and authors of two other studies report non-significant increases in risk for young women with lower body mass indices (Althuis et al., 2003; Tavani et al., 1999). Again, no conclusive evidence exists for an association between weight or body mass index and breast cancer in young women.

Family history

The odds of being diagnosed with breast cancer are 2.4-5.6 times higher for young women with a first degree relative (mother or sister) and 1.6-2.8 times higher for women with a second degree relative (grandmother, aunt, niece, or half-sibling) who had been diagnosed with breast cancer (Althuis et al., 2003; Chilvers et al., 1989; Hill et al., 2002; Jernström et al., 2005; Mayberry, 1994; McCredie et al., 1998; Negri et al., 1988; Pike et al., 1981; Rosenberg et al., 1996; Tavani et al., 1999; Wingo et al., 1991). Authors of one study, conducted in Sweden reported that the odds of developing breast cancer before the age of 40 years if a sister had been diagnosed with breast cancer were 6.6 times the odds of developing cancer if a sister had not been diagnosed (Rebora, Czene, & Reilly, 2008).

Authors of a study conducted in the USA reported that the odds of breast cancer were 3.2 times higher for women whose mother was diagnosed with breast cancer before the age of 50 years, and 1.7 times higher if their mother was diagnosed after the age of 50 years, compared with women whose mothers had never been diagnosed (Althuis et al., 2003). Similarly, the odds of breast cancer were 23 times higher for women with a family history of early onset breast cancer (first or second degree relative diagnosed at 40 years or younger) and 2.8 times higher if the relative was diagnosed when they were older (Lynch, Watson, Conway, Fitzsimmons, & Lynch, 1988).



In two studies, the odds of a woman younger than 40 years of age developing breast cancer if a family member had ovarian cancer were 2.7-3.0 the odds compared to someone without a family member with ovarian cancer (Hill et al., 2002; Jernström et al., 2005). Of note, neither of these estimates were adjusted for the impact of other variables, including family history of breast cancer.

Authors of three studies reported that women born to older mothers (40 years or older) were more likely to develop breast cancer compared with women born to younger mothers, with two reporting a statistically significant trend (Innes et al., 2000; Weiss-Salz et al., 2007). These studies also report that being born to an older father (40 years or older) was a risk factor for breast cancer in younger women even after adjusting for the mother's age (Innes et al., 2000; Weiss-Salz et al., 2007). A third study (Troisi et al., 2013) did not detect an association between maternal age and their offspring's odds of breast cancer and did not report on father's age as a risk factor.

Reproductive factors

There is an association between parity (bearing offspring of >20 weeks gestation) and early onset breast cancer. In five of the six studies that compared them, the odds of breast cancer were lower (OR 0.77-0.88) for women who bore at least one child compared to women who had never carried a child (Chilvers et al., 1989; Clavel-Chapelon et al., 1995; Jernström et al., 2005; Pike et al., 1981; Tryggvadottir et al., 2002). Only one study reported an increased risk of breast cancer in women who had borne children (Tavani et al., 1999).

The age at which women bear children is also associated with breast cancer, with significantly higher odds for women who were older at the birth of the first child than for women who are younger than 20 years old at the time. Compared with women who had children as adolescents, women who had never/not yet borne a child had 1.1-2.1 times higher odds of having early onset breast cancer (Althuis et al., 2003; Chilvers et al., 1989; Tavani et al., 1999). There appears to be an increased risk for breast cancer the longer a woman delays childbearing.

Among parous women (women who carried a fetus for at least 20 weeks) those who bore their first child at 20-24 years of age had 1.02-3.2 times higher odds while women 25-29 years had 1.13-4.2 times higher odds, and women who were 30 years or older had 1.1-5.3 times the odds of breast cancer than women who had given birth as an adolescent (Althuis et al., 2003; Chilvers et al., 1989; Clavel-Chapelon et al., 1995; Mayberry, 1994; Negri et al., 1988; Tavani et al., 1999; Tryggvadottir et al., 2002; Warner et al., 2013).

Young women who have given birth *and* breastfed their child are at lower risk of breast cancer than mothers who have not breastfed their child. The odds of breast cancer is 5-22% lower in women who have breastfed their child compared with women who have not, with longer durations of breastfeeding being more somewhat protective (Chilvers et al., 1989; Mayberry, 1994; McCredie et al., 1998; Tryggvadottir et al., 2002; UK National Case-Control Study Group, 1993; Wingo et al., 1991). Of note, many of the studies have too few women who breastfed longer than 12-18 months to provide stable estimates beyond that duration.



There is a seemingly contradictory possibility of higher estrogen levels during pregnancy being linked to a *transient* increase in the risk of developing breast cancer. Authors of one study conducted between 1983 and 1994 reported a significant trend in the risk, with Italian women having given birth less than three years prior to interview having 3.8 times higher odds of breast cancer than women giving birth twelve or more years prior (Tavani et al., 1999). Another study reported that Australian women who gave birth within the previous year had a non-significantly higher trend in the risk of breast cancer (McCredie et al., 1998). Two other studies reported a non-significantly lower risk of breast cancer in young women in the USA. The first showed a lower risk in women who had given birth in the previous year compared with women giving birth eight or more years previously (Althuis et al., 2003) while the second showed a lower risk in women giving birth in the previous five years compared with women giving birth 10-15 years previously. Both had adjusted for the participant's age in the analysis. A Danish study showed that women with breast cancer who had a family history of breast cancer had a larger risk of being diagnosed within five years of a child's birth compared with those without a family history (Wohlfahrt, Olsen, & Melbye, 2002). No conclusions can be drawn from this contradictory evidence.

There was no association between early onset breast cancer and a history of spontaneous or induced abortions in five of six reviewed studies (Althuis et al., 2003; Mahue-Giangreco, Ursin, Sullivan-Halley, & Bernstein, 2003; Mayberry, 1994; Tavani et al., 1999; Wingo et al., 1991). Authors of an early study, conducted with women diagnosed in 1972-1978, stated that women with breast cancer were more likely than women without breast cancer to report having an abortion prior to their first full-term pregnancy but these results have not been replicated in subsequent studies (Pike et al., 1981).

Other factors

Radiation exposure was assessed in two studies, with authors reporting 1.5-2.6 times higher odds of breast cancer in women who were exposed to three or more X-rays to the chest or neck (Hill et al., 2002) or five or more chest X-rays (Andrieu et al., 2006) before the age of 20 years compared to women with no exposure or exposure only to dental X-rays. Girls and young women exposed to radiation resulting from the atomic bombs dropped in Japan during World War II had a 13-fold increased risk of breast cancer prior to reaching 35 years of age when exposed to a 1 sievert equivalent dose of radiation (Tokunaga et al., 1994). Also, authors of a recent review of studies following young women who received radiation to treat Hodgkin's lymphoma reported that the risk of breast cancer is highest for those treated at a young age (younger than 14 years old) and then declines somewhat (Alm El-Din, El-Badawy, & Taghian, 2008) with the association limited to patients irradiated before the age of 30 years. The elevated risk of breast cancer becomes significant five years after treatment with radiation, but is highest 15 or more years after treatment.

Although drinking alcohol increases the risk of developing breast cancer in older women, none of the six studies in women younger than 40 years of age found a significant association (Althuis et al., 2003; Chilvers et al., 1989; Innes et al., 2000; McCredie et al., 1998; S. J. Smith, Deacon, Chilvers, & UK National Case-Control Study Group, 1994; Tavani et al., 1999). Three studies showed a non-significant increased risk with an increasing number of alcoholic drinks consumed per week while the other three showed an inconsistent trend (increasing for some amounts and decreasing for larger amounts).



Researchers postulate that the duration of exposure is too short to determine an association, if one exists.

Only one study, conducted with young Italian women in the 1980s and early 1990s, reported studying the relationship between other (non-alcohol) dietary exposures and early onset breast cancer (Tavani et al., 1999). The authors report a significant (OR: 0.57) decreased risk for breast cancer in women with more than eight servings of raw vegetables per week. However, with no corroborating evidence, this result should be interpreted with caution. A systematic review of diet and breast cancer, using research from women diagnosed at any age, found no conclusive associations between fruit and vegetable consumption, meat intake, dietary fibre or dietary carbohydrate intake and breast cancer and a suggestive, but not conclusive, link between dietary fat and breast cancer (Mourouti, Kontogianni, Papavagelis, & Panagiotakos, 2015).

Four studies reported that young women with breast cancer were more likely to have smoked cigarettes than young women without breast cancer, although all associations were non-significant (Althuis et al., 2003; Mayberry, 1994; McCredie et al., 1998; S. J. Smith et al., 1994). Only one study reported a negative association between smoking and breast cancer in young women. In that study, women who had ever smoked had lower odds of early onset breast cancer than women who had never smoked, even after adjusting for other factors associated with breast cancer incidence in young women (Jernström et al., 2005). None of these associations were large and the associations were not statistically significant. Thus, no conclusions can be drawn from the studies.

One study conducted in the United Kingdom showed that, after adjusting for other risk factors, the odds of women with breast cancer having been exposed to second-hand smoke both in their childhood home and as an adolescent/adult were about 3 times higher than the odds for women without cancer (S. J. Smith et al., 1994). Although this result was statistically significant, no other studies have reported the association in young women.

Two studies compared the odds of breast cancer by level of physical activity with one reporting significantly lower odds of breast cancer with increasing weekly levels of life-time physical activity (Bernstein, Henderson, Hanisch, Sullivan-Halley, & Ross, 1994) while the other reported no association between physical activity level and breast cancer in young Australian women (McCredie et al., 1998). No conclusions can be drawn from these disparate results among young women.

No studies have been conducted to assess the association between stressful life events and early onset breast cancer. A meta-analysis of results from eight separate studies of women of all ages found no association between negative or stressful life events and breast cancer incidence (Santos et al., 2009), which is in accordance with two previous meta-analyses on the subject.

Bisphenol A is an endocrine-disrupting chemical that may mimic natural hormones. It is often used in plastic containers and the lining of canned goods. It is possible that prolonged exposure to estrogen through oral contraceptives, hormone replacement therapy, or environmental sources such as plastics containing bisphenol A may be a risk factor for some cancers.



However, it is extremely difficult to measure exposures some of which may occur during prenatal periods. A study comparing Korean women with (average age of 46 years) and without breast cancer found no difference in the blood levels of bisphenol A (Yang, Ryu, Jeon, Kang, & Yoo, 2009). No other studies have attempted to measure the association.

Conclusions

There is good evidence to support the association of several factors with higher incidences of breast cancer in women younger than 40 years old, including:

- Age, with the incidence increasing as women get older
- Family history of breast or ovarian cancer
- Oral contraceptives, with higher rates when they start before the age of 20 years and with longer durations of use
- Repeated radiation exposure to chest area
- Benign breast disease
- Young age (younger than 11 or 12 years old) at menarche
- African heritage
- Having no children or delayed childbirth
- Not breastfeeding child/children

There is some, but limited evidence to support an association between early onset breast cancer and being born to parents who were 40 years or older at delivery.

There is no evidence to support the association between healthy lifestyle choices and the risk of breast cancer in young women. However, in older women, obesity, alcohol consumption, and smoking are risk factors for breast cancer while physical activity and a healthy diet (high in fruits and vegetables and low in red and processed meats) are protective (Dieterich, Stubert, Reimer, Erickson, & Berling, 2014). The lack of evidence in younger women may be related to a shorter duration of exposure to the risk/protective factors along with difficulty in accurately measuring these factors during childhood and adolescence.



Promotion of Breast Cancer Awareness

According to Steven Narod, MD, Canada Research Chair in Breast Cancer (Narod, 2012), it is unlikely that eliminating risk factors will prevent breast cancer in young women. More effort into promoting breastfeeding, improving early detection and earlier/correct diagnosis, expanding genetic screening (and research into same), and improved/appropriate chemotherapy for younger women is more likely to produce meaningful results than reducing exposure to some of the few modifiable risk factors.

The Centres for Disease Control and Prevention in the USA hosted a three-day meeting of experts in 2011 to discuss the opportunities for research and health communication regarding risk factors, prevention, early detection, and survivorship of young women with breast cancer (Buchanan, Roland, Rodriguez, Miller, & Fairley, 2013). At that meeting, they discussed the need to educate young women about their individual risk, their family history, risk even without a family history, and risk in the absence of genetic mutations within the family. These experts also suggested guidelines for physicians regarding young women with a history of breast cancer, those at high risk, and those at average risk of breast cancer, along with clear definitions of what constitutes high risk.

Increasing awareness of breast cancer in young women

Researchers in British Columbia developed two two-minute long, youth-informed, sex-specific “YouTube”-style videos to raise awareness about the link between cigarette smoking and premenopausal breast cancer, one for girls and one for boys (Bottorff et al., 2014). The video for girls, available at <https://www.youtube.com/watch?v=jN8alidGceQ>, was rated by 73 girls with an average age of 15.6 years. They agreed that they had learned something new (78%), it was easy to follow (86%), and 43-52% said they would share the link or “Tweet” about it to their friends. The video for boys was also highly rated with 79% learning something new, 87% finding it easy to follow, and 66% saying they would share it with their friends. The same researchers ran nine focus groups with women 15-24 years of age (both smokers and non-smokers) from British Columbia and New Brunswick (Bottorff et al., 2010) to determine their level of knowledge about the link between smoking and premenopausal breast cancer and, after presenting some Canadian data, to determine their reactions to the information. The focus groups attendees suggested that messaging be about protecting others, factual, and available to everyone (not just young females). These researchers also conducted a critical analysis of 32 breast cancer awareness campaigns available as of December 2008 and targeting young women recommended that messages not objectify the female body and that young women be given the opportunity to provide feedback and input into message design (Haines et al., 2010).

A 2011-12 survey of women attending a southwestern college in the USA (94% were younger than 40 years) determined that 44% used the internet to actively seek information about breast cancer while 74% received information passively through the internet, 69% via magazines, and 59% through television (Kratzke, Amatya, & Vilchis, 2014). Most (99%) used a cell phone and about half of those surveyed said they would be interested in receiving free applications for breast self-examination or texts messages about breast cancer prevention with women who felt less adept at breast self-examination being more likely to be interested in an application and text messaging.



Fairley (Fairley, 2011) describes the “BodyTalk” smartphone application developed by the Centre for Disease Control’s Advisory Committee on Breast Cancer on Young Women to disseminate breast cancer information to women younger than 40 years old. No evaluation of the project has been published to date.

Evaluations of the *Team Shan* breast cancer awareness campaigns targeting women 15-29 years of age, physicians and other healthcare providers, and the general public have been conducted in several regions across Canada since 2008. Evaluations were conducted in 2008 for the Southwestern Ontario campaigns in secondary school, post-secondary school, and community sites, 2011 for a campaign in Calgary Alberta post-secondary schools, in 2012 for an expanded campaign in Calgary and the first year in a postsecondary site in Saskatchewan, and in 2013 and 2014 in Alberta, Saskatchewan, and Manitoba (Team Shan, 2008, 2011, 2012, 2013, 2014). Campaign activities include interactive media (website, Facebook group), paid advertisements (billboards, public transit system advertisements), and print media (posters, printed brochures) and in 2008, an information package was mailed to family physicians. In post-campaign surveys, all campaigns were shown to increase the level of knowledge about breast cancer facts, risk factors, self-help recommendations, and symptoms. Following the campaigns, the percent who had no knowledge of breast cancer in young women was reduced to 2.5-8.8% of respondents. Also, 54.3-65.2% were aware of the facts, 60.1-68.2% of the symptoms, 37.8-54.3% of self-help recommendations, and 60.1-70.9% of the risk factors for breast cancer in young women. Although the strategies used to promote awareness varied by campaign, advertisements on transit systems (44.8-71.9%), in bus shelters (27.9-49.1%), and on billboards (28.1-46.2%) were the most frequently recalled of the paid advertisements; posters (28.8-65.1%) were the most recalled print material, and FaceBook (10.8-21.7%) was the most often recalled interactive media source for Team Shan/breast cancer in young women information. The top three messages recalled from the campaigns were that breast cancer can happen at any age (43.7-63.6%), self-help recommendations/get checked (12.9-31.1%), and awareness/seriousness of the disease (11.8-20.8%). The campaigns have reached tens of thousands of young women across Canada, with 82-93% of post-secondary school respondents recalling the Team Shan campaign. Following the 2013-2014 campaign, 44% of respondents indicated they were planning to get checked for lumps/changes in their breasts either by self- or clinical examination (see <http://teamshan.ca/publications>).

Increasing awareness and skills for self-detection of breast cancer in young women

Formal screening programs using mammography, low-energy X-rays, for the detection of breast cancer are conducted in Canada for women 50-69 years old and in the European Union, for women ranging from 40-50 up to 59-74 years of age, depending on the country (Altobelli & Lattanzi, 2014). The incidence of breast cancer is sufficiently low in women under the age of 40 years to conclude that the risks of mammography outweigh the benefits. The Canadian Task Force on Preventive Health Care does *not* recommend either clinical breast exams or self-examination for women 40-74 years old and at average risk of breast cancer since there is no evidence to indicate that either practice reduces mortality from breast cancer (see <http://canadiantaskforce.ca/ctfphc-guidelines/2011-breast-cancer/clinician-cbe-bse-recommendation>).



Further, the 2001 Canadian Task Force recommendations stated that there was a lack of evidence to evaluate the effectiveness of self-detection practices for breast cancer in women younger than 40 years (Baxter & Care, 2001). However, the Public Health Agency of Canada recommends “breast awareness”: knowing your body, watching for changes, and contacting a healthcare provider with concerns (Public Health Agency of Canada, 2009). Similarly, the American Cancer Society recommends clinical breast exams every three years for women starting in the 20s as well as knowing how your breasts normally look and feel and reporting changes to a healthcare provider (see <http://www.cancer.org/healthy/findcancerearly/cancerscreeningguidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer>). The National Health Service/Public Health England and Australian health department also advise breast awareness: knowing what is normal so irregularities can be detected and medical advice sought (see <http://www.cancerscreening.nhs.uk/breastscreen/breastawareness.html> and <http://canceraustralia.gov.au/publications-and-resources/position-statements/early-detection-breast-cancer>).

Common symptoms of cancer (any type) in adolescents and young adults include lumps in the breast, neck, abdomen or testicle, abnormal pigmented skin lesions, headache, neurological deficits (loss of balance, numbness, muscle weakness, etc.), lethargy, and isolated pain or a lump in an arm or leg (Canadian Cancer Society, 2009b). Delays in diagnosis and treatment may be reduced if individuals are aware of unusual changes to their breasts, testes or skin and seek prompt medical attention (Canadian Cancer Society, 2009b). In fact, 95% of breast cancers in women 35 years of age or younger who participated in an Ontario study were self-detected, being detected by themselves or their partner (Figueirde et al., 2007). Similarly, in a study from the USA, 71% of breast cancers in women younger than 45 years old were self-detected with another 9% detected during a clinical breast exam (Coates et al., 2001). An early study of breast awareness/self-examination determined that women who practiced regular self-examination detected lumps when they were smaller than women who never performed self-examination, 1.97 versus 3.59 cm (Foster et al., 1978). Yet, only 41% (Burak & Boone, 2008) to 55% of American (Kratzke et al., 2014) and 56% of Australian (Budden, 1999) young women regularly perform breast self-examination.

Authors of a survey of women attending a southwestern college in the USA reported that 45% scored high on their level of knowledge of breast cancer, 49% felt they were adept at breast self-examination and 55% of them conducted it regularly (Kratzke et al., 2014). In another study in the USA, 89% of 1047 college women surveyed (83% were younger than 40 years old) responded that breast self-examination is important, but only 42% of felt sure or very sure that they were doing breast self-examination correctly. Breast self-examination was less likely to be practiced by younger respondents (20-29 years old) than older ones while it was more likely to be practiced by women with positive attitudes about breast self-examination (i.e., it is important, can help with early detection, ability to self-detect). Of those surveyed, 70% had had a clinical breast examination during their last physician visit (Early, Armstrong, Burke, & Thompson, 2011).



Student nurses under 40 years of age volunteered for a pre-test post-test study about breast self-examination in Australia in the 1990s (Budden, 1999). Although 96% of the 71 students agreed that young women need to perform regular breast self-examination, only 52% felt confident with the technique to use and 45% in their ability to detect a lump, which correlates with the fact that 56% regularly performed breast self-examination.

An educational intervention study conducted in New York state in colleges/universities (79% were 18-22 years old) and the community centres (85% were 50 years or older) consisted of 35-40 minute presentations covering the epidemiology of breast cancer, disease biology, and risk factors (Zeinomar & Moslehi, 2013). Significant increases in knowledge, from less than 40% at baseline to almost 80% after the presentation, were noted for the college/university respondents with similar increases in knowledge for the community group. Researchers did not assess behavioural or attitudinal attributes.

Young women, aged 17-23, from a private American university rated as being in the pre-contemplation stage of behaviour change about breast self-examination (18% of those screened), were split into three groups: consciousness-raising writing group, action-oriented group, and control group (S. L. Smith, Kloss, Kniele, & Anderson, 2007). A nine-minute breast self-examination instruction video and a knowledge quiz were given to participants in all three groups. Following this, women in the consciousness-raising group wrote about their thoughts and feelings about breast cancer and breast self-examination while participants in the action-oriented group created a plan for performing breast self-examination and members of the control group were dismissed. One week later, participants in the two experimental groups repeated and refined their respective exercises. Five weeks after the initial session, participants from all three groups returned to complete the knowledge quiz with a reported increase in motivation to practice breast self-examination in both experimental groups, but higher ratings for action and preparation in the action-oriented group. The authors conclude that the exercise of designing a plan, including plans to overcome obstacles, prompts further engagement in people in the contemplation and pre-contemplation phases of behaviour change.

Female adolescents aged 11-19, both high risk (family history of breast cancer or BRCA1/2 mutation) were interviewed about their knowledge and perception of risks for breast cancer in teens. Adolescents with a family history were more likely than other teens to report family history as a risk factor but no more likely to report non-familial risk factors for breast cancer. Most (>83%) did not recall hearing about BRCA1/2 genes, which did not differ by familial risk. A higher percent (76%) of adolescents with a family history perceived themselves at higher risk for breast cancer than those without a known history (22%). Most (70%) of teens reported that you could prevent breast cancer by screening mammograms or self-exams, being healthy (diet, exercise, etc.), and avoiding exposures (tobacco, alcohol, etc.). Mothers were the most frequently (≥89%) reported source of information about breast cancer in this group of participants.



Recommendations

Based on the information highlighted in this literature review, the authors suggest the following:

1. *Inform the public about the potential risk to young women.*
 - a. Although breast cancer is uncommon in women younger than 40 years of age, they, their parents, and medical practitioners need to know that cancer, including breast cancer, is *not* a disease limited to older adults.
2. *Educate the public about the risk factors for breast cancer in young women.*
 - a. Although many young women develop breast cancer without having any known risk factors, those with known risk factors (such as a family history) need to understand their increased risk and communicate them to their healthcare providers.
 - b. Many risk factors for young women cannot be changed or are not easily modifiable making it difficult to avoid exposure. However, women at higher risk of breast cancer should consider the benefits and harms of exposure to known risk factors.
 - c. Some risk factors (such as family history) are not within an individual's control. However, maintaining a healthy lifestyle by following Canada's Food Guide, maintaining a body mass index in the normal range (18.5-24.9), being physically active, smoke-free, and alcohol-free may reduce the risk of breast cancer in the long term.
3. *Educate healthcare providers about the potential risk of, and risk factors for, breast cancer in young women*
 - a. Healthcare providers must understand the incidence of breast cancer and the risk factors for breast cancer so women of all ages, including young women, can be appropriately and adequately screened and tested.
4. *Promote breast awareness AND early communication of changes to healthcare providers.*
 - a. Knowing what is normal for each individual can lead to early recognition of potential health problems if the information is then communicated to healthcare providers.
 - b. Promoting breast awareness, including breast self-checks, is important for young women, most of whom should not receive screening mammograms.
5. *Health promotion campaigns should:*
 - a. Provide basic, accurate, credible health information.
 - b. Encourage appraisal of reliability of information and accurate perceptions of personal risk.
 - c. Build competence in essential skills such as knowing your body or body self-awareness .
 - d. Encourage communication of changes or concerns with parents and healthcare providers .
 - e. Use strategies designed to personalize information, maintain interest, and motivate behaviour.
 - f. Include input and feedback from the target audience (adolescents and young adults).



- g. Include parents of adolescents and young adults and healthcare providers as secondary target groups.



Appendix

Methods used for the review

This literature review was completed using search methods developed and refined by the Cochrane Collaboration with assessment of the literature using methods recommended by the Canadian National Advisory Committee on Immunization. The last 20 years' of published data were reviewed. Key words, MeSH terms, and synonyms were used to search key databases (MedLine, EMBASE, and Web-of-Science) on June 1, 2015. Following the search of databases, additional information was retrieved through hand searching reference lists of key articles (e.g. reviews) and using feedback from TeamShan staff of other known publications and/or material.

Review staff screened the available data in a brief summary of the citations including: study design, population and sub-groups, sample size, cancer type, and topic area (incidence, mortality, risk factors, program evaluations). All articles/sources determined to be relevant following the screening (above) were downloaded and/or otherwise retrieved from libraries, journal sites, and/or other sources by the research staff. Only those meeting the inclusion criteria upon review of the article title and/or abstract were retained. A flow chart outlining the number of titles included and excluded, including the rationale for exclusion is available in the appendix of the final report. All articles were scanned to determine their continued eligibility. Those meeting eligibility were reviewed for their quality and to abstract the data required to inform decisions. The reviewers independently assessed each publication, providing a table summarizing (as a minimum) each study's study design (e.g. RCT, cohort, case-control), population studied (e.g. age group, setting), size of study population studied, outcome measures (e.g. incidence, mortality, knowledge, behaviour), results with confidence intervals or statistical tests of association, as available, ranking of level of evidence by study design, and evaluation of study quality.

Each study was ranked by design: randomized control trial (I), controlled trial without randomization (II-1), cohort (II-2), case-control (II-2), multiple time-series (II-3), descriptive studies & case reports (III). All studies will be assessed, using standardized checklists (e.g., CONSORT <http://www.consort-statement.org>) for the quality of the evidence. Studies of poor quality will not be used to inform recommendations. Quality will be rated as good if it meets all design-specific criteria; fair if it does not meet design-specific criteria, but has no fatal flaws; and poor if it has one design-specific fatal flaw *or* an accumulation of lesser flaws (Harris et al., 2001). The strengths and limitations of every study were considered in the development of the final report. Only studies of good or fair quality were included in the final report.

Statistical terms

Risk ratios and odds ratios are used compare the likelihood of an event (e.g., breast cancer) occurring in two groups. A risk ratio (RR) is the *probability* of an outcome (e.g., cancer) in people who all have a similar exposure (e.g., smoking), divided by the probability of that outcome in people who are not exposed. An odds ratio is the *odds* of a person who has the outcome was exposed divided by the odds that a person without the outcome was exposed. A RR or OR of one (1) means that the likelihood is the same for both groups (e.g., $18/50 \div 36/100 = 1$ or $1:3 \div 2:6 = 1$).



A ratio above one indicates a positive association between the exposure and the outcome (i.e., increased risk of cancer) while a ratio below one indicates a negative association (i.e., lower risk). Whenever available, adjusted estimates of association (odds or risk ratios) are presented meaning that the estimates have been adjusted for the effect of other variables of interest (e.g., age at diagnosis or family history of breast cancer).

A 95% confidence interval (CI) is used to estimate what the statistical estimate (e.g., RR or OR) would be if the study was repeated in another population who share similar exposures and demographic traits. If the CI crosses the null value (i.e., 1.0 for RR and OR), it signifies that if the study were conducted in 20 other populations, no association between the outcome and exposure would be expected in at least 19 of those studies (e.g., 95% CI: 0.8-2.2). If both the lower and upper bound of the CI are on one side of the null value, the likelihood of an association is higher (e.g., 95% CI: 1.4-1.8) or lower (e.g., 95% CI: 0.1-0.9).

Potential years of life lost (PPYL) is a measure of the “relative” impact of a specific cause of death taking into account the age of the person who died. For example, if a person dies at the age of 35 and the average age of death in that society is 85 years, the result is 50 years of potential life lost. Meanwhile, if that person was 80, the potential years of life lost is 5, giving it much less weight. This measure is typically expressed as a rate per 100,000 people in the population.

Age standardized rates are used to compare the rates of occurrence or mortality, among other things, across time or geography. By using age group-specific rates from each time or place and then weighting them to a standard underlying population structure, the rates can be compared without concern that the differences in the age of the comparative populations are causing any differences.

Limitations of the review

As with any study, this literature review has limitations. The major limitations are:

- The amount of published research available regarding risk factors for breast cancer in young women is limited. As such, some articles include women slightly older than 40 years old and the results may not be as applicable, particularly to the youngest women.
- Although we attempted to review all of the relevant articles, we cannot be sure that all have been retrieved.
- Authors attempt to quantify interactions between different risk and protective factors through study design and statistical means (e.g., adjusting for them, as noted earlier). However, when there are many different factors at play, it requires a very large sample size to adjust for all factors.
- Researchers don't know all of the factors affecting the incidence of breast cancer, especially in younger women. As such, they may not be measured, or may not be measured accurately in studies.



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