Ontario
Cancer Care Ontario
Action Cancer Ontario

Cancer Risk Factors in Ontario

Reproductive and Hormonal Factors (Female)

REPRODUCTIVE AND HORMONAL FACTORS (FEMALE)

Risk factor/exposure	Cancer	Direction of association	Magnitude of risk*	Strength of evidence
Parity	Cervix	↑	1.07[a]	Established
	Breast	↓	0.89–0.92[b]	
	Endometrium	↓	0.65[c]	
	Ovary	↓	0.92[d]	
Breastfeeding	Breast	↓	0.98[e]	Established
Later age at first birth/full-term pregnancy	Breast	↑	1.10–1.23[b]	Established
	Cervix	↓	0.95[a]	
Later age at menarche	Breast	↓	0.65–0.93[b]	Established
	Endometrium	↓	0.72–0.76[c,f]	
Later age at menopause	Breast	↑	1.20–1.32[b]	Established
	Endometrium	↑	1.53–2.20[c,f]	
Oral contraceptive use	Liver†	↑	1.45–1.57[g]	Sufficient
	Breast‡	↑	1.24[h]	
	Cervix‡	↑	1.65[i]	
	Endometrium	↓	0.50–0.65[c,j]	
	Ovary	↓	0.73[k]	
Hormone replacement therapy for menopause	Breast	↑	1.21[l]	Sufficient
	Endometrium	↑	1.44–1.75[f,m]	

Sources: [a]International Collaboration of Epidemiological Studies of Cervical Cancer, 2006; [b]Reeves et al., 2009; [c]Dossus et al., 2010; [d]Tsilidis et al., 2011; [e]WCRF/AICR, 2007; [f]Kerageorgi et al., 2010; [g]Maheshwari et al., 2007; [h]Collaborative Group on Hormonal Factors in Breast Cancer, 1996; [i]International Collaboration of Epidemiological Studies of Cervical Cancer, 2007; [j]IARC, 2007; [k]Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2008; [l]Collaborative Group on Hormonal Factors in Breast Cancer, 1997; [m]Allen et al., 2010

* Risk estimates are relative risks (RRs). The groups for comparison and measures of exposure differ between risk factor/exposures and in some cases between cancers for a given exposure. See text for details.
† In populations at low risk for hepatitis B infection.
‡ Current and recent oral contraceptive use.

Background

» Reproductive factors, such as parity, age at menarche and age at menopause, are closely related and influence the levels of sex hormones (e.g., estrogen, progesterone) circulating in the body.[64]

» Endogenous female sex hormones are produced by the ovaries. Among other functions, estrogen stimulates the development of the breasts and the growth of endometrial tissue. Progesterone plays a key role in preparing the endometrium for pregnancy and also regulates the effect of estrogen.[64]

» The strong connections between reproductive factors, endogenous hormones and exogenous hormones, such as oral contraceptives, make it difficult to disentangle the individual effect of each factor on cancer risk in epidemiologic studies.

PARITY

- Parity is a well-established protective factor for cancer of the breast, endometrium and ovary.[65] In contrast, higher parity *increases* the risk of cervical cancer.
- An inverse dose-response relationship is seen for breast, endometrial and ovarian cancer, and a positive dose-response is observed for cervical cancer:
    - A large UK cohort study found an approximately 10% reduction in risk for each additional birth for the most common histologic types of breast cancer (unadjusted for age at first birth).[66] Several large studies have found an effect of parity independent of age at first birth.[67–69]
    - Compared to nulliparous women, women who had had at least one full-term pregnancy had a 35% reduced risk of endometrial cancer in a large European cohort;[70] risk decreases with increasing numbers of children.[70,71]
    - Ovarian cancer risk was 29% lower for women with at least one full-term pregnancy than for nulliparous women in a large cohort study, with an 8% lower risk per full-term pregnancy.[72]
    - A large international pooled analysis found cervical cancer risk increased 7% per additional full-term pregnancy after controlling for other factors, including age at first birth, age at first sexual intercourse and number of sexual partners.[73]
- For breast and ovarian cancer, some evidence suggests that risk varies depending on the histologic type of the tumour, with a reduced risk more consistently seen for estrogen receptor (ER)-positive than for ER-negative breast cancer[74] and for the most common histologic subtype of ovarian cancer and some rare subtypes.[75]

BREASTFEEDING

- A large meta-analysis conducted by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) found a 2% reduction in breast cancer risk for every 5 months of breastfeeding, additional to the risk reduction from number of births, and controlling for such other factors as age at first birth.[24]
- Some evidence is emerging that breastfeeding lowers the risk of ovarian cancer, although the WCRF/AICR panel concluded that the evidence for this cancer was only limited.[24,76]

LATER AGE AT FIRST BIRTH

- Older age at first birth is a well-established risk factor for breast cancer.[65] In a large UK cohort study, risk increased 10%–23%, depending on histologic type, per 5-year delay in age at first birth.[66] A large review found a more consistent increase in risk with delayed childbearing for estrogen receptor (ER)-positive than for ER-negative breast cancer.[74]
- Later age at first birth decreases the risk of cervical cancer. A large international pooled analysis estimated that risk decreased 5%/1-year increase in age at first full-term pregnancy after controlling for factors, including parity, age at first sexual intercourse and number of sexual partners.[73]

LATER AGE AT MENARCHE

- Later age at menarche has been consistently associated with a reduced risk of breast cancer.[65] A large UK cohort study estimated a 7%–35% decrease in breast cancer risk, depending on histologic type, with every 5-year increase in age at menarche.[66] A large review found older age at menarche more consistently associated with a reduced risk of estrogen receptor (ER)-positive/progesterone receptor (PR)-positive than with ER-negative/PR-negative breast cancer.[74]
- Later age at menarche is also a protective factor for endometrial cancer.[65] This has been confirmed in two large studies (one from the UK and one from the US), with decreases of more than 24% for menarche at age 15 or older compared with menarche at approximately age 12 or younger and decreasing risk with later ages at menarche; one study controlled for body mass index, which is related to both endometrial cancer risk and age at menarche.[70,71]

LATER AGE AT MENOPAUSE

- Late menopause is an established risk factor for breast cancer.[65] A large UK cohort study found a 20%–32% increase in risk, depending on histologic type, per 5-year delay in age at menopause in never-users of hormone replacement therapy.[66] A large international pooled analysis found an approximate 3% increase in breast cancer risk for each year increase in age at menopause.[77]
- Late menopause is a risk for endometrial cancer.[65] Two large cohort studies, one in the US and one in Europe, found risk increases of from 53% to more than 2-fold for menopause of age 55 or older compared with ages less than 45 or less than 50, the risk increasing with older ages at menopause.[70,71]
- For ovarian cancer the results are mixed, with contradictory findings from large cohort studies as to whether late menopause increases risk.[72,75,78]

ORAL CONTRACEPTIVES

- Combined oral estrogen-progestogen contraceptives are classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans (Group 1), on the basis of increased risks for cancer of the breast (among current and recent users), cervix and liver (in populations at low risk for hepatitis B viral infection).[79,80]
- Large international pooled analyses have estimated current users of combined oral estrogen-progestogen contraceptives have a 24% increased risk of breast cancer and a 65% increased risk of cervical cancer compared to never-user.[81,82] Liver cancer risk may be increased by roughly 50% in long-term oral contraceptive users in populations at low risk for hepatitis B infection.[80,83]
- Cessation of oral contraceptive use reduces the associated risk of breast and cervical cancer in a dose-dependent manner, with risk declining over time to no excess risk by 10 years after cessation.[81]
- There is convincing evidence that oral contraceptives reduce the risk of cancer of the endometrium (with the risk for ever-users approximately halved)[79,80] and ovary (with a 27% lower risk among ever-users and further reductions with greater duration of use).[72,84]

HORMONE REPLACEMENT THERAPY FOR MENOPAUSE

IARC has concluded that combined estrogen-progestogen hormone replacement therapy (HRT) for menopause increases the risk of breast cancer, mainly in current or recent users. A large pooled analysis found a risk increase of approximately 2%/year for current or recent use;[77] risk magnitude varies with type of hormone therapy and histologic type of breast cancer.[85–87] HRT use increases the risk of endometrial cancer when progestogens are taken for less than 10 days/month, but not when progestogens are taken daily.[79,80] The broad range in magnitude of increased risk for endometrial cancer among current HRT users reflects different preparations and different durations of use, with risk estimates from less than 2-fold to more than 7-fold.[71,88]

BIOLOGIC MECHANISMS

- High levels of unopposed estrogen appear to be the common exposure in several risk factors considered here; reproductive factors increase total estrogen exposure by resulting in more lifetime menstrual cycles. Exact mechanisms, and whether estrogen is a causal or promoter agent, are not fully understood.[89,90] Breastfeeding may lower risk hormonally by lowering the number of menstrual cycles, and through developmental and other effects on breast epithelium.[24] Developmental effects on the breast may also contribute to reduction in breast cancer risk with higher parity.[89]
- The lowered risk of ovarian and endometrial cancers with oral contraceptive use appears to be associated with atrophic and antiproliferative effects in the endometrium and apoptosis of ovarian epithelial cells.[80]
- Methodologic issues complicate our understanding of the role of several factors associated with increased risk of cervical cancer: higher parity, earlier age at first birth, oral contraceptive use, sexual behaviour and human papillomavirus (HPV) infection. Higher parity and earlier age at first birth appear to have a role beyond simply serving as proxies for increased exposure to HPV. High parity may, for example, be a co-factor affecting the risk of HPV infection and/or its progression to cervical cancer.[73,82]