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GYNECOLOGICAL SURGICAL PROCEDURES AND RISK OF STOMACH, COLON AND RECTAL CANCERS

by

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for the Degree of Master of Science,
Graduate Department of Community Health,
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ABSTRACT

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An exploratory investigation was conducted to examine risk of stomach, colon and rectal cancers in women who had certain common gynecological surgical procedures in Ontario between 1979 and 1993. Person-years were measured until death, a cancer diagnosis, or the end of the study period after cohort linkage to the Ontario Cancer Registry and the Ontario mortality file. The relative risk estimates were calculated by comparing observed cancer events to expected cancer events based on age and calendar period-specific incidence rates of Ontario women.

Risk of stomach cancer was consistently reduced for all procedures. This was also generally true for risk of colon and rectal cancers, although there was individual variation by site and procedure that diverged from a protective effect. Although the results support the hypothesis that the procedures alter cancer risk, the association should be investigated further. This should be done in studies that take into consideration a number of potential confounders and examine more closely lifetime endogenous and exogenous estrogen exposure.

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LITERATURE REVIEW

THE PROCEDURES

The sterilization of women is widely practised today as a form of family planning and for pathologic conditions that require organ or tissue removal. Presently, the only methods available are those that involve surgery on the uterus or fallopian tubes. In the past few decades there has been much debate over whether a hysterectomy or tubal ligation should be performed. Hysterectomy is used for sterilization usually only when there are other conditions that would merit uterine removal, such as bleeding disorders or cervical dysplasia, due to the associated higher morbidity, mortality, and increased cost (Kaser et al., 1985).

Tubal Sterilization

Fallopian tubes can be occluded by partial resection, coagulation, or the application of clips or rings. The procedures can be approached vaginally or abdominally. The vaginal route allows for typical occlusion methods like resection, fimbriectomy or the application of clips, and coagulation. The leading technique has become laparoscopic sterilization that approaches the fallopian tubes via the abdomen. Either bipolar electrocoagulation or clips are used to seal the tubes if done in this way (Wilson, 1995).

Partial resection of the fallopian tubes is achieved by various methods. The most common is the Pomeroy procedure. Other techniques include the Irving and Madlener operations, cornual

resection and fimbriectomy (Kroener operation) which remove a segment of the fallopian tubes (Wilson, 1995). Salpingectomy, however, is the removal of the entire tube, and its purpose is more for the removal of an ectopic pregnancy than to inhibit conception (Kaser et al., 1985).

Electrocoagulation is now the preferred method for laparoscopic sterilization (Kaser et al., 1985). A unipolar method is infrequently used, if at all, due to accidental burns. Bipolar coagulation can be more precisely controlled. This method destroys a longer segment of the tube, approximately 1.5 cm, than many other techniques (Wilson, 1995). Clips and rings were originally thought to be a safe alternative to coagulation with the hypothetical advantage of reversibility, especially rings, which also cause less injury (Wilson, 1995).

Tubal sterilization is reliable, technically simple and relatively safe. The rates of failure and death vary and are dependent upon the choice of the procedure. Failure rates increase as the duration of observation time increases, however Loffer and Pent (1980) estimated rates based on accumulated statistics. They range from unipolar electrocoagulation , 1.5%, to spring clip at less then 5.2%. An older study (Shepard, 1974) produced failure rates consistently less then 1%, except for the Madlener technique (13.5%), and the Pomeroy (4.6%). In general, mortality is not greater than 1 per 100,000 and serious complications are no more than 1 per 1000, with a total morbidity rate of a few percent. Tubal sterilization varies in how it is done, what part of the fallopian tube is altered, and the extent of the damage to the fallopian tube (Kaser et al., 1985).

Hysterectomy and Oophorectomy

The uterus can be removed by way of the vagina or the abdomen. Both approaches have advantages and disadvantages, with morbidity and mortality being comparable, although there are

differences in the rates of various complications (Kaser et al., 1985). Oophorectomy following hysterectomy was sometimes performed, removing a potential source of disease. However, given the potential benefits of retaining the ovaries in premenopausal women, the ovaries are now being retained with the hope that the benefits of continued hormonal function will outweigh the risk of benign or malignant tumours (Kaser et al., 1985).

PROCEDURES AND HORMONE OUTPUT

Women who undergo premature ovarian failure are thought to be at increased risk of osteoporosis and myocardial infarction because of ensuing hormonal changes (Johansson et al., 1975; Centerwall, 1981). In the past it was thought that gynecological procedures such as hysterectomy had no adverse effects on ovarian hormone output and basic function. It is now more appropriate to think that the ovarian environment does change, as does function.

Certain gynecological procedures such as hysterectomy and tubal sterilization are thought to alter the blood supply to the ovary. There is a theoretical explanation for the reduction of estrogen that occurs after a tubal ligation (Cattanach, 1985). The ovarian segment of the uterine artery is close to the part of the fallopian tube that is either occluded or interrupted by tubal sterilization techniques. This would alter the blood supply of the ovary, as only the distal end of the artery going into the ovary would be functional. In fact, it has been suggested that any procedure (including hysterectomy) that would partially obstruct or distort the ovarian artery will produce a similar but reduced effect. After tubal ligation there may be an increase of arterial pressure of up to 200 Pascals at the distal end of the ovary (Cattanach, 1985). The ensuing hypertension would damage the blood supply to the ovary at the microvascular level which would lead to tissue necrosis. It has been speculated that the

reduced blood flow could reduce the delivery of follicular stimulating hormone (FSH) and luteinizing hormone (LH) which would cause the reduction in the production of estrogen (E) and progesterone (P). This reduction in estrogen and progesterone would increase FSH and LH, which is how a perimenopausal state is achieved (Lethbridge, 1992). This explains changes in menstrual flow in women after tubal ligation. The uterus would not be exposed to enough progesterone which could cause a heavy and lengthened shedding of the endometrium.

The production of estrogen and progesterone are dependent on the oxygen-rich blood supply to the ovary. Estrogen production is speculated to be more greatly affected than progesterone because the production of progesterone from cholesterol requires only three enzymatic steps requiring oxygen, whereas estrogen from cholesterol requires seven steps. Thus between 3 and 8 times more oxygen is required to create an equal amount of estrogen compared to progesterone (Cattanach, 1985). Despite a given cause of hormone deficiency and ovarian failure, however, researchers are divided as to whether gynecological surgery does alter hormone output, and if so, to what extent. In general, tubal sterilization and hysterectomy have been evaluated separately in their effects.

Tubal sterilization is thought to cause changes in menstrual function, such as increased pain, menstrual flow and spotting, in some women, due to local hypertension or even the torsion of fallopian tubes and ovaries. This is termed "posttubal ligation syndrome" (Lethbridge, 1992). Problems are defined as irregular cycles, dysmenorrhea, menorrhagia and midcycle bleeding. Findings have been inconsistent, possibly due to reasons such as varied length of time since the procedure. Several studies have indicated the importance of a long period of follow-up to highlight changes that may occur.

The Collaborative Review of Sterilization, a large, prospective, American study of tubal sterilization (Wilcox et al., 1992), provides evidence for posttubal ligation syndrome. Study participants were interviewed immediately before surgery and annually for up to five years after. The authors noted that should tubal sterilization lead to changes, these changes may require time to develop. Within the first year postsurgery, 27% of those interviewed reported high menstrual pain, 41% reported heavy menstrual flow and 7% reported spotting. These results were very similar to what was reported prior to surgery. Five years after sterilization, 35% of participants reported high levels of pain associated with periods, 49% reported heavy or very heavy menstrual flow and 10% reported spotting between periods, all of which differed significantly from the first year results.

Posttubal ligation syndrome can lead to hysterectomy in order to gain relief from painful symptoms. Work by Goldhaber et al. (1993) examined the long-term risk of hysterectomy which sheds some light on the possible effect of tubal sterilization and the importance of time from the procedure. It was found that women who were sterilized were significantly more likely to have a hysterectomy than those in the comparison group (RR=1.35, 95% CI=1.26-1.44). Risk was elevated for those with diagnoses of menstrual dysfunction and pelvic pain (RR=1.88, 95% CI=1.65-2.13). Those who underwent tubal sterilization between the age of 20 and 24 years were most likely to have a hysterectomy (RR=2.45, 95% CI=1.79-3.36), while those in the highest age group, 40 and 49 years, were least likely (RR=0.96, CI=0.72-1.28). The types of occlusion methods were taken into consideration and there was no difference in risk for hysterectomy associated with methods that potentially destroy tissue to varying degrees. After seven years of follow-up, all age groups had significantly elevated risk.

These results are supported by those of Cohen et al. (1987) who measured the risk of

undergoing hysterectomy up to nine years after tubal sterilization in 4,373 women and 6,835 randomly selected controls. Within the first two years there were no differences in the number of hospitalizations for menstrual or gynecological disorders in women aged 25-29 and 30-44 years. Between two and nine years, however, women aged 25-29 at the time of surgery were 1.6 times (95% CI=1.2-2.3) more likely to have a hysterectomy after adjustment for previous gynecological history, marital status, number of physician visits and hospitalizations. Those in the older age group (30-44) showed no increased risk for hysterectomy. Lending support to these observations is another prospective study that looked at long-term risk of menstrual changes after sterilization (DeStefano et al., 1985). Comparisons were made at 6-24 months, 25-48 months, and 49-87 months after tubal sterilization. The prevalence of abnormalities in the sterilized group did not appear to differ from the control group until 2 years after surgery. At 49-87 months there was a significant increase of nearly three times the number of abnormal cycles in the sterilized group.

Hormone research has been conducted after tubal sterilization to elucidate the main cause of problems, with some focus on the type of sterilization performed. Many of these studies have limitations and the results should be interpreted with caution. For example, many only measure hormone output for a year and do not consider age, parity or contraceptive use prior to sterilization. As well, these findings, although relevant, do not distinguish between reasons for risk of menstrual disturbances like reduced blood flow, hypertension or tube torsion. The findings also suggest that if women experience changes, these may not be immediate.

One of the most recent studies (Hakverdi et al., 1994) evaluated 43 women, aged 25-40 years, before and after tubal sterilization. Midcycle hormone levels and endometrial biopsies were taken before sterilization and at 3, 6, and 12 months after surgery. At 3 and 6 months no significant

difference was observed. There was a significant increase ($p<0.05$) of FSH, as well as LH and estrogen ($p<0.001$) one year after surgery, and a significant decrease in progesterone ($p<0.001$). As well, 13 women (30.2%) had anovulation at this time. This work is supported by Donnez et al. (1981) who compared three groups of women for progesterone levels: a control group (65 women with average age 32.2 years), a group sterilized with clips (35 patients, average age 33.4 years) and a group sterilized by the Pomeroy procedure or coagulation (13 women, average age 34.1 years). Progesterone levels were below 10ng/ml in 54% of women in the group that had coagulation or Pomeroy ligation, compared to 20% in those that used clips and 12% in the control group ($p<0.001$). This helps to explain the hypothesis that different types of sterilization alter ovarian function to different degrees. The clip causes less tissue damage and may better preserve the uteroovarian artery.

Radwanska (1982) did not examine the different forms of sterilization, but did examine women who had abnormal menses (14 women) prior to tubal sterilization, along with a group experiencing normal menses (9 women) prior to tubal sterilization and a control group (28 women). These procedures were done an average of five years (range, 1-9 years) before hormone measurements were made. A significant difference ($p<0.01$) in progesterone levels was detected between the controls and those with abnormal menses. Overall, 78% of those with prior abnormal menses, 44% of those with normal menses and 15% of controls had lower than normal levels of progesterone.

On the other hand, there have been reports of no dysfunction whether the outcome be menstruation or hormone production. Bhiwandiwala et al. (1982) showed no association when different laparoscopic occlusion techniques were compared in 24,439 women. Women were followed most often for 6 and 12 months, and some for 18 and 24 months. Most women did not experience

any change in menstrual patterns. If a change occurred, the direction of change was equally likely to be an increase or decrease in menstrual flow. Between 79% and 86.5% of women maintained regularity of flow, which depended on the type of occlusion technique performed.

Ring and clip laparoscopic sterilization were examined by Thranov et al. (1992) for hormonal and menstrual changes. Blood samples were taken before and 3, 6, and 12 months after surgery. They reported no changes in menstrual patterns. They did find that luteal phase progesterone was significantly reduced at the third month ($p<0.012$). They concluded that laparoscopic sterilization by rings or clips does not interfere with menstrual patterns or ovarian function since there were no other changes in hormone levels. This gave support to earlier work (Hague et al., 1987; Alvarez et al., 1989; Rivera et al., 1989) that indicated no effect of tubal sterilization. Alvarez et al. (1989) evaluated the Pomeroy and the Uchida techniques, chosen because of the different risks of affecting circulation as they destroy different amounts of fallopian tube tissue. Measurements at 2 and 6 months for LH, FSH, E and P did not differ from those taken before the procedure, except for the significant increase in progesterone at 2 mos. ($P<0.003$) after Uchida ligation.

Hysterectomy has been independently evaluated. This literature is important as it can help elucidate if changes women report after tubal sterilization can simply be due to hormonal changes due to reduction in ovarian function rather than to torsion of the fallopian tubes. Again, follow up from the procedure is often limited and the reported results vary, some showing significant changes to menstruation or hormone levels while others do not.

One of the most recent studies (Bukovsky et al., 1995) compared residual ovarian function in women who had hysterectomy with preservation of one or both ovaries. The 40 subjects were randomized into either group, following informed consent. Hormones (FSH, LH, E) were measured

before surgery,1 week, 1, 3, and 6 months postoperation. All those with both ovaries had normal hormone levels 6 months after hysterectomy. Compared to those who had one ovary removed, a significant difference in the levels of FSH ($p<0.003$), LH ($p<0.004$), E ($p<0.05$) were observed. At six months those with conserved ovaries showed no ovarian dysfunction, although 35% of those with only one ovary did. Two explanations were given: that the ovarian blood supply was impaired; or that unilateral oophorectomy reduces the ovarian follicles by half, leading to impaired functioning after a few months in women with border-line normal functions. This report does demonstrate that there may be an acute effect of sterilization.

A retrospective study by Siddle et al. (1987) provides evidence for blood supply impairment. Identified were 229 women who had undergone spontaneous menopause and 90 women who had a hysterectomy with bilateral ovarian conservation. The mean age of menopause, defined as the time of symptoms due to a drop in estrogen levels, or ovarian failure, for the nonhysterectomized women was 49.5 years whereas those who had surgery became menopausal at 45.4 years of age. A relationship between age at hysterectomy and age at time of menopause was statistically significant ($r=0.6$, $p<0.001$). To strengthen this analysis, the researchers divided the women into two groups. The first included women who became menopausal at or before age 44 (33 women) while the other included those at least 45 years of age (57 women). A statistically significant correlation was found in the youngest group ($r=0.62$, $p<0.001$), but it was not observed in the older women ($r=0.32$, $p>0.05$). Also measured was the interval between surgery and menopause. Ovarian failure (menopause) occurred within 2 years for 34% (31 patients), of which 20 were under the age of 45. Within four years 46 women became menopausal, and 25 of them were under the age of 45. However, in some, this happened as much as 15 years later. The data show that women are not

equally affected. Some appear not to have had any symptoms, as 46% (44) did not experience symptoms until at least five years later. Overall, 40 (44.4%) of the 90 hysterectomized women had ovarian failure by 45.4 years of age compared with 29 (13%) of the 229 women who did not have surgery.

A review of the literature on ovarian function following hysterectomy was done by Siddle et al. (1987) and considered only women who were under 45 years at the time of surgery with either unilateral or bilateral ovarian conservation. They noted that all authors reported a subgroup of women with early ovarian failure, averaging 23.5% of the sample. The studies were not easily compared due to the differences in study design (e.g. length of follow-up). Despite this, the studies show that some women do indeed have premature ovarian dysfunction.

So far, research shows that there may have been impairment, although absolute hormone levels are not known. The much cited study by Stone et al. (1975) looked at the acute effects of hysterectomy on the production of estrogen and progesterone by the ovaries and compared these findings to a control group of women who had undergone laparoscopy for diagnostic purposes. A drop in circulating estrogen levels was noted on the second day after surgery, 60pg/ml to 20pg/ml, which was significantly different from the preoperative levels of estrogen ($p<0.01$). The changes lasted for more than three days, and were significant for all women with hysterectomy. Normal levels were found 3-4 weeks later. The control group showed no significant difference in circulating levels at any point. Thus, the changes were likely related to the manipulation of the region rather than the stress of surgery on the body in general. The authors also felt that the alteration was only acute and the ovary readjusted from a possible acute reduction in blood flow.

To correlate clinical, endocrine and histologic data, Souza et al. (1986) performed bilateral

ovarian biopsies in 25 women immediately before and twelve months after hysterectomy. As well, serum levels of estrogen and progesterone were measured. No changes were detected in serum hormone levels. Histological changes, however, were observed that could have resulted from lymphatic or circulatory changes.

Certain research does not support the thesis that ovarian function is altered. Ellsworth et al. (1983) found no change in 20 women, all under 45 years of age at the time of hysterectomy for cervical carcinoma. Of the twenty, 15 conserved both ovaries and 5 only one. The biochemical and clinical measures were made between 3 months and greater than 5 years after surgery, with an average interval of 4.8 years. The authors believe that 80% of women retained ovarian function because they maintained premenopausal hormone levels and had cyclic ovarian function. The other 5 (20%) were thought to have had failure prior to surgery as they had required estrogen replacement therapy.

A more general examination of sterilization was carried out, in which women in a hysterectomized and a control group were evaluated for estrogen and progesterone (Corson et al., 1981). Operations were done at least 6 months before assessment (range not given). No significant difference was observed, although the groups contained fewer than ten women each. A regression analysis was done for the estrogen and progesterone relationship. There was no significant correlation between hormone levels in either of the groups. This, as well as the large standard deviations for hormonal data, indicates cautious interpretation due to the small number of women and the need to analyse more samples over a greater time interval.

Overall the findings indicate that there may be hormonal changes associated with tubal ligation and hysterectomy that could adversely affect some women. Further investigation is certainly required

to examine estrogen levels specifically after a long period of follow-up. The research on women who had tubal sterilization indicates that posttubal ligation syndrome is likely to include hormone reduction in some women. This may only be evident many years after the procedure, rather than immediately, since tissue damage to the ovary is necessary. The literature also indicates the potential for ovarian failure after hysterectomy. This may occur in a subgroup of women and perhaps only after a certain length of time following surgery. The fact that this may happen to women who had a hysterectomy lends support to posttubal ligation syndrome. Hysterectomy is less disruptive to the ovarian environment but may cause some of the same changes to hormone levels as tubal sterilization. Hence, this syndrome may be due to tube torsion, but may also have hormonal cause. The number of women possibly affected and the amount of alteration of hormone output require further investigation.

NORMAL CHANGES- THE MENOPAUSAL OVARY

There is very good clinical evidence that after menopause there is a reduction in the amount of estrogen production. During a normal menstrual cycle, serum estradiol levels fluctuate from 50 to 350 pg/ml and estrone from 30 to110pg/ml (Smith et al., 1994). The fluctuations are not apparent in postmenopausal women so that the mean estradiol level is 12 pg/ml (5 to 25 pg/ml range) and the mean estrone level is 29 pg/ml (20 to 70 pg/ml). In postmenopausal women the ovary contributes minimally to this estrogen supply. It is the conversion of some testosterone and mostly estrone to estradiol that is the source of estrogen. The adrenal gland is the major source of estrone as ovarian secretion is minimal. The adrenal gland does not directly contribute but rather it is the aromatisation of androstenedione which occurs in fat, muscle, liver, bone, brain, fibroblasts and hair roots. Although it is not known to what extent each cell type contributes, it is known that fat cells are

responsible for 30-40% (Smith et al., 1994).

Progesterone levels in premenopausal women ranges from 0.2-0.7ng/ml in the follicular phase of the menstrual cycle to 3-21 ng/ml in the luteal phase. Progesterone is also compromised after menopause as levels are only 30% of the concentrations seen in young women in the follicular phase of the menstrual cycle, which is approximately 0.17 ng/ml. The source of this small amount of progesterone may be adrenal secretion. As well, there is reduction in the secretion of androgens and an increase in gonadotropin (LH and FSH) levels at perimenopause and postmenopause.

CHARACTERISTICS OF WOMEN WHO HAVE GYNECOLOGICAL SURGERY

Defining specific characteristics of women who have had the gynecological surgeries being investigated, is made difficult by the dearth of literature, especially with respect to procedures other then hysterectomy. Despite the lack of research, some conclusions have been drawn especially for hysterectomy.

Women with hysterectomy have been examined the most reflecting the women of Australia, Britain, Denmark and the USA, in comparison to women who have had other gynecological surgery. Studies suggest that correlates of hysterectomy are: income, education, parity, oral contraceptive use, tubal sterilization for contraception, race and urban place of residence. A negative relationship of increasing income with prevalence of prior hysterectomy has been reported (Koepsell et al., 1980). Studies of consultations in general practice show that patients from higher socioeconomic (SES) groups have longer consultations and receive more explanations (Cartwright et al., 1976). Therefore, women who are better educated and from a higher social class may receive more discussion, making them less likely to opt for surgery and more likely to choose less radical treatment (e.g. tubal

sterilization). It has been reported that women of lower SES are less likely to receive regular gynecological exams (Howe et al., 1986; Mamon et al., 1990). They may not present with gynecological problems, such as uterine fibroids, until the problem is too severe to be treated without hysterectomy (Kjerulff et al., 1993). Another explanation for the impact of education could be that there may be greater menstrual difficulty in women of lower socioeconomic groups since certain occupations may have an impact on menstrual irregularity (Settnes et al., 1996) like those of the pharmaceutical industry or where women are exposed to nitrous oxide . Some studies report a positive association of parity because of birth-related injuries, the desire to stop childbearing, or the biased recommendation by doctors to women who already have a number of children (Koepsell et al., 1980). Parity is inversely related to socioeconomic status and positively related to risk of hysterectomy (Kuh et al., 1995).

It should be noted that unilateral oophorectomy and unilateral tubal sterilization were performed for reasons other than contraception. Women who have these procedures may differ from those in other procedure subgroups. As well, tubal sterilization is voluntary and an informed choice should be made by those women; thus, they are likely from higher SES groups. Oophorectomy is most likely related to a medical condition requiring ovary removal so perhaps, as with hysterectomy, women tend to have run out of other treatment options. These women may be more likely to be of lower SES.

Race, although known to be associated with income and education, was not strongly related to hysterectomy in one study (Kjerulff et al., 1993), although in another, women who had undergone hysterectomy were more often black (Meilahn et al., 1989). Luoto et al. (1992) reported regional differences in risk for hysterectomy with risk increasing in women living in an urban environment.

Another study also found this difference (Santow et al., 1992).

What has not been examined is hormone replacement therapy (HRT). One can speculate that HRT may have the same impact on tendency to have gynecological surgery as oral contraceptives in that women will tend to go to the doctor more frequently and therefore be better informed. On the other hand, women who use HRT do so because of the hormonal changes resulting from surgery; hence any increased medical surveillance, due to menopausal symptoms or to have HRT prescriptions assessed, would come post-surgery (Roos, 1984).

Use of oral contraceptives (OCs) may also affect the risk of hysterectomy because OC users tend to visit the doctor more frequently, are asked more frequently questions about symptoms and thus might be less inclined to have the surgery (Santow et al., 1992). Past and current users undergo more Papanicolao (pap) smears than other women (Dickinson et al., 1988).

Finally, tubal sterilization may affect risk of hysterectomy if it replaces hysterectomies done for contraceptive reasons rather than for a medical condition. Thus, tubal sterilization reduces the likelihood of having a hysterectomy. However, due to posttubal ligation syndrome, women may chose to have a hysterectomy for relief of pain and abnormal bleeding (Cohen, 1987; Goldhaber et al., 1993).

THE DISEASES

Stomach Cancer

Incidence, Survival and Trends

Stomach cancer incidence within Ontario is the ninth most prominent cancer, with 1060 newly diagnosed cases in 1989 (McLaughlin et al., 1995). It is the twelfth most common cancer in women. As well, within Ontario there are regional differences in incidence.

There has been a decline in stomach cancer incidence, which is more prominent in women than in men (Holowaty et al., 1995). Incidence increases with age, with most cases occurring in individuals over the age of 45 (McLaughlin et al., 1995). For the period 1964-1968 the age-standardized incidence rate per 100,000 was 8.41 for women. By 1989-1991, this had decreased to the age-standardized rate of 4.48 in women. This type of reduction applies to all age groups. Risk for stomach cancer is 60% higher in men than women.

The prognosis for stomach cancer is poor, the five year relative survival rate being 24%, over all ages (McLaughlin et al., 1995). The median survival time is the same for both males and females. Survival is dependent on age, as younger individuals have a better prognosis, and on anatomic location. Those with a tumour located in the lower portions of the stomach have better prognosis compared to those with a tumour in the upper part of the stomach.

Risk Factors

In the etiology of stomach cancer, diet is a prominent factor. Individuals with a higher intake of vegetables and/or fruits have been documented to be at lower risk; beta-carotene is correlated with a high fruit and vegetable diet, and may be protective (Neugat et al., 1996). Other environmental

factors associated with increased risk are nitrates in drinking water, and in pickled and cured foods. High salt, retinol and carbohydrate intake increases cancer risk (Kono et al., 1996). With respect to areas in the stomach, infection with *Helicobacter pylori* and gastroenterostomy have been associated with cancer of the lower stomach (Nomura, 1996). Alcohol and tobacco use, and hiatal hernia, have all been associated with cancer of the upper stomach. Exposure to certain compounds in occupational settings, such as asbestos and wood dust, have been associated with increased risk as well (Nomura, 1996). Also associated with an increase in risk is family history, some types of chronic gastritis and certain host factors such as type A blood (Nomura, 1996). Endogenous sex hormones have been shown to provide some protection however they are still being investigated (LaVecchia et al., 1994; Palli et al., 1994).

Colon and Rectum Cancers

Incidence, Survival and Trends

In Ontario, colorectal cancer is the second most common cancer in women (Holowaty,1995). The age-standardized incidence rates per 100,000 have slightly decreased from 33.74 in the 1960s to 32.17 in 1989-91. The incidence rates are clearly influenced by age, with the majority of cases occurring after the age of 65 (64%). For men, the incidence is 40% higher than women.

The relative five-year survival rate for colorectal cancer is 54% (McLaughlin et al.,1995). In general, age plays a very small role in cancer survival, with younger individuals having only a slightly increased relative survival rate than older individuals. Survival is dependent upon the anatomic location of the cancer. The best prognosis is for cancer of the anus and anal canal, then colon, and finally rectum, with five year relative survival rates of 63%, 54% and 48% respectively, for males and

females combined (female only rates unavailable). The difference between survival rates between males and females is very small.

Risk Factors

Due to the misclassification that often occurs in distinguishing the lower sigmoid colon from the upper rectum, risk factors are often described for these two sites combined. The factors may differ, however, in terms of importance and degree.

Dietary components affect risk for colorectal cancer. High fat and meat consumption as well as low intake of fibre, vegetable and fruit increase risk (Potter et al., 1993). Other factors that increase risk are disorders like familial adenomatous polyposis and those that cause chronic inflammation. Low physical activity and obesity may also increase risk. Protection may be incurred in women who have had a large number of children (Schottenfeld et al., 1996). Also being investigated is the role of endogenous hormones as a risk factor. Specifically, estrogen and how it may alter bile acids which put one at risk for colorectal cancer or may interact with estrogen receptors in the colon and rectum (Potter, 1993).

SEX HORMONES AS RISK FACTORS

Stomach

Sex hormone receptors have been shown to be important in the etiology of certain cancers such as breast and endometrial, as well as in survival (Smith et al., 1975; Osborne et al., 1980). Sex hormone receptors such as estrogen (ER) and progesterone receptors (PR) have been characterized by several techniques in gastric cancer tissue as well as in the normal mucosa (Tokunaga et al., 1983;

Sica et al., 1984). A study conducted by Wu et al. (1990) examined ER and PR levels in gastric cancer tissue. They found that 31.2% (5 tumours) had PR and 75% had ER. These values are higher than those reported by others. Sica et al. (1984) reported that 14 tumours (25%) in 56 specimens had PR and 14.3% ER. Tokunaga et al. (1983) and Urehara et al. (1987) obtained similar results to those of Sica et al. (1984). Although the results are generally in agreement, those of Wu et al. (1990) indicate that there are varying degrees of detection. Also important to consider is the type of stomach cancer studied. For example, Urehara et al. (1987) analysed the scirrhous type of carcinoma, whereas other researchers included varying histological types, which may have different characteristics. Evidence supports the fact that estrogen and progesterone receptor levels are not correlated (Wu et al., 1990). Recent research indicated that the presence of PR is independent of ER in cancer cells (Wu et al., 1994). The estrogen-regulated pS2 protein is also present in normal, benign and neoplastic mucosal tissue (Luqmani et al., 1989). Given these observations, it has been suggested that the growth of tumours in the stomach may be hormone-regulated. Research is now focused on the effects of estrogen and progesterone and some hormone antagonists. In studying the effects of hormones on carcinogenesis, the focus has primarily been on estrogen.

To date, detailed characteristics of ER have not been completely elucidated however, Matsui et al. (1991) revealed some of the activity of such receptors. Binding to the receptors was inhibited by estradiol and not by other hormones, which indicates specific binding to estrogen. This proved that the estrogen receptors in gastric cancer have as much specificity and affinity to estrogen as do those found in endometrial cancer and breast cancer. Thus hormone therapy that is similar to that used in the treatment of breast and endometrial cancer may be effective in individuals who have ER-positive gastric cancer.

Estrogen has been shown to affect gastric cancer cell growth differently by either stimulating growth (Harrison et al., 1989), inhibiting it (Furukawa et al., 1982) or causing no change (Wu et al., 1994). An early study (Furukawa et al., 1982) investigated the effects of endogenous sex hormones in rats fed MNNG, the carcinogenic agent N-methyl-N-nitro-N-nitrosoguanidine, for four months. There were four treatment groups: males, females, castrated males and castrated females. A year after MNNG was administered, 81% of male rats, 0% of female, 29% of castrated male and 5% of castrated female rats had stomach cancer. Compared to the male group at 12 months, the others exhibited a significant difference ($p<0.05$) in incidence. The disparity in incidence was less at 4 and 8 months. The results suggest a protective effect of female hormones and perhaps that male hormones facilitate carcinogenesis. The rates of stomach cancer in Ontario indicate that risk is 60% higher in men than women (Holowaty et al., 1995).

More recently, the effect of tamoxifen and estrogen receptor status on survival was investigated by Harrison et al. (1989). One hundred individuals (73 male, 27 female) were randomized into a group to receive tamoxifen until death or to be in the untreated control group, matched for gender and stage. The results show that stage did not affect receptor status. Those who were estrogen receptor negative (54.2%, 53% male and 36% female) survived significantly longer ($p<0.03$). Those who were positive for receptors and were treated with tamoxifen had a significantly shorter survival time ($p<0.009$). The presence of the receptors, or positive staining, indicated a poor prognosis in both sexes ($p=0.03$) compared to those with negative staining. The results also indicate that tamoxifen has no beneficial effect and the trend indicated that there was a decrease in survival time in the tamoxifen-treated patients of either sex.

These results are opposite those of two Japanese studies (Kitaoka et al., 1983, Kojima et al.,

1986). Kitaoka et al. (1983) reported that the cumulative 3-year survival rates of those receiving chemo-endocrine therapy for stomach cancer after gastrectomy were higher (43.3%) than those who received chemotherapy alone (5.6%) (p-value not given). As well, 2- and 3- year survival rates for curatively resected cases were both 100% for those receiving tamoxifen compared with 68.4% and 16.3%, respectively, for those not receiving this treatment ($p<0.01$). This was supported by Kojima et al. (1986) who showed better prognoses in patients with stomach cancer for those administered tamoxifen. These patients also received chemotherapy, and it is thought that tamoxifen made the tumours more susceptible to the effects of the other agents. The reason that survival in the study of Harrison et al. (1989) was reduced is not clear, although Harrison et al. (1989) suggests that subsequent research may include the reduction in circulating estrogen concentrations.

Later research conducted by Wu et al. (1994) examined cell growth both in vitro and in vivo, in the presence of steroid hormones and antagonists. In vitro cells were exposed to estrogen, hydrocortisone, progesterone and/or tamoxifen, and RU38486. In vivo, progesterone, RU386, megestrol acetate and a combination of progesterone and RU386 were administered to mice with grafted tumour cells. In all circumstances, none of the compounds had an effect on cell growth. The authors put forward the idea that hormones and hormone antagonists may regulate gene expression, but these genes may not be directly related to cell growth in vitro or in vivo, or hormone regulation may be time dependent (Furukawa et al., 1982; Harrison et al., 1989).

An evaluation was also conducted on how survival is influenced by ER status (Kojima et al., 1991). A 5-year survival rate of 62.7% was observed for ER-negative stomach cancer patients whereas in ER-positive patients it was 15.7% ($p<0.001$). This is opposite to what would be anticipated in individuals with breast cancer where the prognosis is better for those with receptor

positive tumours. This result may indicate that stomach is a nontarget organ in that it is not meant to be affected by estrogen, but is nonetheless. This study only analysed whether the ER status of cancer tissue was correlated to survival in patients. An analysis including other factors, like stage of disease and age of the patient, would have been more useful. Whether ER and PR are related to pathological status needs to be examined in further depth.

The biological role of progesterone may be important in the development of cancer since research has shown a presence of progesterone receptors in all gastric cancers and 93.4% of gastric normal mucosa (Wu et al., 1990). Other hormone receptors, like androgen and gastrin receptors, are being quantified as well to provide a more general understanding of how hormones and receptors can affect cancer risk. Investigations until now have not explored progesterone or other endogenous hormones.

Given this information on the possible role of estrogen, two case-control studies were conducted to evaluate how reproductive history and hormone exposure affect risk of stomach cancer. The first was an Italian study (Palli et al., 1994) which provided some direct evidence that post-menopausal women with gastric cancer had a significantly shorter fertile period (menarche to menopause) than did controls. Age at menarche, number of live births, number of abortions and age at first pregnancy were all not statistically significant. There was a significant inverse relationship, however, between age at menopause and stomach cancer risk. The authors did not report a linear relationship, but the reduction was seen among women reporting menopause after 45 years of age versus before age 45 with odds ratios ranging from 0.6 (95% CI=0.4-0.96) for the stratum 45-49; OR=0.5 (95% CI=0.4-0.8) for the age stratum 50-54 and OR= 0.6 (95% CI=0.3-1.0) for the highest age stratum, greater than 55 years. A significant inverse relationship was also found when years of

fertility were examined, giving an odds ratio of 0.6 (95% CI=0.4-0.9) for more than forty years of fertility.

This study's primary focus was on diet, and only limited information was collected on reproductive factors. No data were collected to reflect the type of menopause, the use of exogenous hormones and the type of abortions (spontaneous or induced). The authors also mentioned that while the years of fertility and age at menopause are correlated, these could affect the risk for stomach cancer by different, but unstated, hormonal mechanisms.

An Italian case-control study (LaVecchia et al., 1994) also incorporated information on exogenous hormone use. Age at menopause had a significant inverse relationship with stomach cancer and the multivariate odds ratio (OR) for women over the age of 53 was 0.6 (95% CI= 0.3 to 1.0) relative to those whose menopause was before the age of 45 years. Years of fertility was tested, but a nonsignificant trend in cancer risk was observed. None of the odds ratios was significant, although women who had at least 39 years of fertility had an OR=0.66 (95% CI= 0.4-1.1) compared to those with less than 32 years of fertility. Age at menarche, ever-use of oral contraceptives, ever-use of hormone replacement therapy and age at first birth were all nonsignificant. There was a significant increasing trend in risk for stomach cancer as the number of births increased ($p<0.05$).

In summary, the laboratory research suggests a definite role of endogenous estrogen, although the type and extent of the effect are debatable. The epidemiologic research is more clear and suggests an inverse relationship of endogenous estrogen exposure, as measured by age at menopause and parity, and stomach cancer risk.

Colon/Rectum

There are two possible mechanisms of how female sex hormones affect colon carcinogenesis. The first is the bile acids hypothesis. This suggests that colon carcinogenesis is influenced by the amount, composition and bacterial degradation of bile acids in the colon (McMichael et al.,1985). The second mechanism is based in basic medical science. The idea is that hormones influence colon and rectal cancer risk because of the presence of estrogen and progesterone receptors and estrogen receptor mRNA in normal, premalignant and malignant tissue (Alford et al., 1979; D'Istria et al.,1986; Francavilla et al., 1987).

Based on the first hypothesis, the proximal and distal colon can be separated as having different risk for cancer. The undigested fibre in the colon undergoes fermentation and degradation in the proximal colon for a longer period, and is in a much more liquid state. As well, the transit time in the proximal colon is much slower, so the faecal-mucosal contact and reabsorption of the bile acids differ between proximal and distal colon. McMichael and Potter (1985) write that the risk for proximal cancer is heightened due to changes in bile acid metabolism under certain conditions, including being female. They state that the incidence of cancer of the cecum and ascending colon in women is generally 10-20% greater than men at all ages, regardless of the overall incidence in the population. This is in contrast with an inverse relationship for the descending and sigmoid colon.

Although this trend may be due to behaviour, it may also be due to biological differences between the sexes (e.g. hormone composition). It is known that estrogens influence lipoprotein metabolism, bile acid synthesis and bile composition. Prior to menopause women have lower plasma cholesterol than men of the same age, as well as a higher concentration of high density lipoprotein (HDL) (McMichael et al., 1980; Pennington et al.,1981; Wahl et al., 1983), which is cleared by the

liver from the blood. This HDL is then secreted in bile. Cholesterol saturation of bile appears to vary inversely with HDL concentration in plasma (Thornton et al., 1981). Some evidence exists to support the idea that there are sex differences in bile acid synthesis and composition, because in men taking 30ug of ethinyl estradiol daily for seven days, the lipid profile in bile changed (Anderson et al., 1980). As well, the ratio of secondary bile acids (bacterially degraded) to primary bile acids is greater in women than men, which may be due to a number of factors, including pH and bowel transit time (Fisher et al., 1973).

Evidence to support this hypothesis comes from related research. For example, work has been done to look at risk for colon cancer after cholecystectomy which seems to increase risk due to the altered pattern of bile secretion and recirculation (Linos et al., 1981). An inverse relationship between cholesterol in blood and cancer risk was found.

The role of endogenous and exogenous hormones on the composition of bile acids is being elucidated. Most epidemiologic research is focused on reproduction and exogenous hormone use rather than endogenous hormone exposure, other than pregnancy. Early work observed that nuns had an increased incidence of colon cancer (Fraumeni et al., 1969). As well, an association between breast and colon cancer (Howell, 1976) was documented. From this and other studies a hypothesis was generated by McMichael and Potter (1980) that higher parity, early age at first birth, and use of oral contraceptives (OC) was associated with a reduced risk of colon cancer due to changes in hormones and bile acids. Overall, it was stated that progesterone, pregnancy, and high dose oral contraceptives lower plasma HDL, lower clearance of cholesterol by the liver and reduce bile acid production, thereby reducing risk. Conversely endogenous estrogens lower plasma cholesterol and increase bile acid production, thereby increasing risk. A review of the literature (Potter et al., 1993)

indicates that higher parity is only associated with reduced risk in older women, but that age at first birth is not. As well, use of hormone replacement therapy and oral contraceptives do seem to be associated with a reduction in risk. While epidemiologic and laboratory research has examined the hypothesis that a woman's hormonal milieu can alter risk, little focus has been on age at menopause, time of fertility, or even the type of menopause (natural or artificial).

Sex hormone receptor research is focussed on the estrogen receptor and its potential role in carcinogenesis. Most often colon cell lines are investigated, rather than colon and rectal cell lines. If both types were used then there could be an indication if differences exist in receptor status and response for the colon and rectum. The most recent work done examined the effect of tamoxifen on induced colon tumours in rats (Ziv et al., 1997). The animals (n=131) received weekly subcutaneous injections of DMH, the carcinogenic agent 1,2-dimethylhydrazine-HCl, and half also received tamoxifen daily for up to 28 weeks. Those given tamoxifen had 41% fewer (p=0.07) tumours (51.5% vs. 72.7%). It was also noted that the estrogen receptor level was significantly lower in the cancer tissue compared with the normal tissue. Receptors were not detected in the mucosal tissue in the control group. Although the result is not statistically significant this does justify continued research of this type.

The effect of tamoxifen and fenrentinimide (an analogue of vitamin A which can inhibit growth in breast cells) on colon and rectal cell lines was observed in vitro (Ziv et al., 1994). Both compounds, together or separately, significantly inhibited cell growth of colon cancer cells compared to control cells. In combination, tamoxifen and fenrentinimide inhibited rectal cancer cell growth more than they did separately, in a certain line of rectal cancer cells. Still, another line of rectal cancer cells was observed to have a significant increase in growth when treated with tamoxifen and

fenrentinimide ($p=0.02$) compared to untreated cells; this was not observed when the compounds were used separately. Singh et al. (1994) demonstrated that premalignant colon cells had a 16% increase in cell growth in the presence of estrogen for 10 days ($p<0.01$). The number of breast cancer cells increased by 53% in 6 days of exposure. The colonic malignant cells showed no change. The authors suggest that in vivo, estrogen has the greatest effect on normal and premalignant cells and little influence on those that are malignant. This is supported by the work of Harrison et al. (1989) and Watson et al. (1993).

Evidence that estrogen plays a direct role in colon cell growth is supported by research that created a matching RNA strand (antisense) to the ER mRNA which inhibited synthesis of ER in a colon cell line (Xu et al., 1994). The researchers were able to show that estrogen-stimulated growth was inhibited. This suggested that the ER-mediated growth effect of estrogen is directly involved in the cell growth of the particular cell line used.

The epidemiologic evidence to date concerning endogenous hormones is weak and inconsistent. The expectation is that there may be a protective effect with reduced hormone exposure based on the laboratory evidence. Age at menopause has been examined with the results being mainly inconclusive. A weak protective effect for late age at menopause was observed, which is contrary to what is expected. For example, the case-control study by Franceschi et al. (1991) found the odds ratio (OR) of colorectal cancer for those with menopause occurring at or after 50 compared to those who had menopause before age 45 is OR=0.4 (95% CI=0.2-1.0). This effect is somewhat similar with that observed by the prospective study of Wu et al. (1987), although the estimates are not significant. The results show little risk difference for the age groups, possibly because the age groups may be too close together to see an effect. Kvale et al. (1991) compared

those over age 53 at menopause to those under age 46 which may be a better comparison, although the findings are not more conclusive. An OR=1.11 (95% CI=0.78-1.60) was estimated for colon cancer and OR=0.89 (95% CI=0.52-1.51) for rectal cancer, comparing the older women to those younger at menopause.

Proximal and distal sites of colorectal cancer have been examined separately with respect to age at menopause. Peters et al. (1990) found that those below the age of 48 had a significantly reduced odds of distal colon cancer compared to those 48-52 (OR=0.40, CI=0.16-0.93) whereas the proximal sites yielded an OR=2.27 (95% CI=0.93-5.53) for the same age strata. Gerhardsson de Verdier et al. (1992) examined menopause, but compared those who became menopausal at or after fifty years of age to those before 50, which is a converse comparison to the other mentioned results. The team found an OR= 0.9 (95% CI=0.6-1.3) for colon cancer; OR=1.0 (95% CI=0.6-1.6) for rectal cancer; OR=0.8 (95% CI=0.5-1.3) for proximal colon cancer; and OR=1.0 (95% CI=0.6-1.7) for distal colon cancer, which are inconclusive, but may suggest that there may be no effect of age at menopause. Again, 50 years of age may be too low to effectively illustrate an effect of menopause on risk.

Menarche has also been examined as a measure of hormone exposure. Gerhadsson de Verdier et al. (1992) compared women who began menstruating at or after age 13 with those who began at an earlier age. Again, the results were not statistically significant. An OR=0.7 (95% CI=0.4-1.2) for colon cancer; OR=0.8 (95% CI=0.4-1.3) for rectal cancer; OR=0.7 (95% CI=0.4-1.3) for proximal colon cancer and OR=0.8 (95% CI=0.4-1.6) for distal colon cancer were observed. These results indicate that late menarche may be protective which is coherent with the study hypothesis. Kvale et al. (1991) examined menstrual history by more finely stratifying age at menarche and age at

menopause and found that age at menarche and menopause were not significantly associated. An odds ratio was estimated comparing the most extreme age groups. Age at menarche for those 17 years and above versus 12 years and younger produced an OR=0.87 (95% CI=0.63-1.20) for colon cancer and an OR=0.99 (95% CI=0.61-1.59) for rectal cancer.

Negri et al. (1989) separately studied colon and rectal cancers and found no trend or significant results for age at menarche for rectal cancer. Colon cancer risk however, was significantly reduced for those with age at menarche of 15 and over (OR=0.51, 95% CI=0.27-0.98) compared with those under age 12. The pattern of the effect was also significant (p-value for trend <0.01). Another study examining risk among Chinese females in North America and in China (Wu-Williams et al., 1991), however, found inconclusive evidence of a relationship between age at menarche and colon cancer in women from either continent. Those in North America had an overall RR=1.08 (95%CI=0.9-1.2) and those in China had a RR= 0.95 (95%CI=0.8-1.2). However, age at menarche was negatively associated with risk of rectal cancer in China (RR=0.87, 95% CI=0.8-1.0) but not North America (RR=1.04, 95% CI=0.9-1.20). Similarly, Chute et al. (1991) stratified age at menarche into one year age groups from age 10-16 years and found no significant effect for increasing or decreasing age at menarche on cancer risk for colon, rectum and colon subsites.

Gynecological procedures have been examined to a limited degree. The case-control study of Jacobs et al. (1994) found that, unstratified by age, there was a statistically nonsignificant increased risk for colon cancer following hysterectomy (OR=1.15, 95% CI=0.69-1.94) and following hysterectomy and bilateral oophorectomy (OR=1.43, 95% CI=0.73-2.80). Those under 45 years at time of hysterectomy had an OR=1.38 (95% CI=0.76-2.49), while those who had a hysterectomy and bilateral ovariectomy had an OR=2.19 (95% CI=0.84-5.71) compared to those with no hysterectomy

of the same age. Those at or above the age of 45 who only had a hysterectomy had OR=0.76 (95% CI=0.32-1.79) and those who also had a bilateral oophorectomy had OR=1.04(95% CI=0.46-2.38). Wu et al. (1987) also evaluated the type of menopause, adjusted for age, for its effect on colon cancer. Hysterectomy without bilateral oophorectomy and bilateral oophorectomy with or without hysterectomy were compared to natural menopause. A simple hysterectomy yielded a RR=1.16 (95% CI=0.6-2.4) and those with ovary removal had a significantly elevated RR=2.16 (95% CI=1.1-4.4). The reason for this finding is unclear. The examination of menopause using gynecological surgery indicates opposition to the study hypothesis in that women generally appear to be at increased risk for colorectal cancer rather than at decreased risk.

The results of work to date provide some documentation on colorectal cancer and hormones. Inconsistencies remain, since it is expected that early menopause would be protective, as would be fewer fertile years. The best evidence uses menarche as a measure of hormonal exposure. The results are not strong but provide some indication that there may be a relationship, whereby reduced hormone exposure is associated with reduced cancer risk.

Summary

The literature suggests that certain gynecological procedures may cause a change in the hormonal output of the ovaries. From the literature, tubal sterilization should produce the greatest effect compared to either no surgery, or to a unilateral tubal sterilization followed by hysterectomy. The extent that a unilateral oophorectomy and unilateral sterilization would alter hormone output is unclear. A hysterectomy with bilateral salpingo-oophorectomy will obviously cause the total truncation of hormonal production.

The literature also suggests that there may be a hormonal influence in the etiology of stomach, colon and rectal cancers. Endogenous estrogen appears to be protective for stomach cancer while the opposite seems to occur for colon and rectal cancers. The extent of the influence of estrogen is unknown and the mechanisms uncertain. In the case of colorectal cancer, both hormone receptors and bile acids may affect risk, while estrogen receptors are likely the only means by which estrogen can promote cancer in the stomach.

It is important to continue to assess how ovarian hormones may affect cancer risk. This study provides an opportunity to evaluate the hypothesis that gynecological surgery influences risk of stomach, colon and rectal cancers, possibly through the mechanism of altering endogenous estrogen.

METHODS

The data for this investigation were obtained from a population-based cohort of all women who had undergone a gynecological surgical procedure between April 1979 and March 1993 in Ontario. This historical cohort was originally compiled to observe the risk of ovarian cancer after certain gynecological surgical procedures, for which the data collection and record linkages had already been completed (Kreiger et al., 1997).

DATA COLLECTION AND RECORD LINKAGES

Females of all ages, including infants and children, were identified through the Hospital Medical Records Institute (HMRI) as having had gynecological surgery from April 1979 to March 1993. HMRI provided data for all in-patient procedures performed from April 1979; women who had out-patient/same-day surgery were only reported beginning April 1990. The initial HMRI records were obtained through the Ontario Ministry of Health (MOH). This initial data file was evaluated for completeness. Greater than 95% completeness was achieved for surname, first name, complete birth date and hospital discharge date. As for OHIP/HIN number and procedure date, these were estimated to have 86% and 63% completeness, respectively.

Three probabilistic linkages followed which were performed using Automatch (Jaro, 1993). The first was an internal linkage of the HMRI/MOH records where a single identification number was assigned to women with more than one procedure/hospital admission. The linkage then gave a total of 858,926 records, which represented women who may have had multiple, but unique records. The second linkage took the HMRI/MOH file and linked it with the all-causes mortality file. This

contained the death certificate information for all Ontario residents who had died between 1978 and 1994. This mortality file was also reviewed for completeness. Surname, first name, entire birth date, entire death date and age were greater than 99% complete. Finally, the HMRI/MOH file was linked to all cancers diagnosed from April 1979 to December 31, 1993 and recorded in the Ontario Cancer Registry (OCR). Data elements such as name, sex and birth date and age at diagnosis have greater than 99% completeness, and OHIP/HIN number has greater than 95% completeness for records in the registry. As well, the capture of cancer events from reporting sources has been estimated at greater than 95% for this population-based cancer registry (Robles et al., 1988).

METHODS SPECIFIC TO PRESENT STUDY

Selection of the Study Cohort

Women were included if they had had one or more specific gynecological procedures and were between the ages of 15 and 64 at the time of the procedure. The surgeries are: a unilateral or bilateral oophorectomy, any type of tubal sterilization or salpingectomy, a hysterectomy, or a hysterectomy with bilateral salpingo-oophorectomy.

Women who had had a procedure within six months of a cancer diagnosis, or a procedure that followed a cancer diagnosis, were excluded. The study cohort initially contained 858,926 records. After the selection for procedures, 781,329 records were left. The age exclusion further reduced this to 736,216. Diagnoses within six months of the procedure were excluded. Thus the number of cohort members decreased again. The final number varied with sites being examined as the exclusion criteria were applied to the cohort separately for each cancer under consideration. There were 734,905 records in the stomach cancer cohort to a minimum of 733,568 records in the

cohort examining both colon and rectal cancers.

If procedure date was missing and discharge date could not be assigned as a proxy date, then these women were also excluded. Duplicate records or records with missing birth date were also excluded.

Variables Collected

Date of birth and procedure date and type were obtained from the HMRI data. Cancer events were available from the Ontario Cancer Registry, while dates of death were available from the mortality file. Potential confounders (e.g. socioeconomic status and hormone replacement therapy) aside from age at the surgical procedure, could not be measured within this data set.

Exposure Definition

Six groups were derived from the cohort. These groups were identified through the classification of procedures from the HMRI records, according to the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (Statistics Canada Health Division, 1986) (see Appendix I). They were: unilateral oophorectomy, bilateral oophorectomy, unilateral tubal sterilization, bilateral tubal sterilization, hysterectomy, and hysterectomy and bilateral salpingo-oophorectomy (see Table 1.1). Due to the small number of women identified for the bilateral oophorectomy group ($n < 1000$ for women who ever had, and $n < 100$ for women who only had the procedure), it was excluded.

Table 1.1 CCSP* Procedure codes that yielded the specific groups for analysis

Procedure Group	Procedure Codes
Unilateral Oophorectomy	7720, 7730, a combination of 7852 and 7720
Unilateral Tubal Sterilization	7810, 7852, 7892
Bilateral Tubal Sterilization	7821, 7822, 7831-7839, 7841-7849, 7853, 7859
Hysterectomy	8020-8060
Hysterectomy plus Bilateral Salpingo-oophorectomy	a combination of 8030-8060 and 7751

* Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (Statistics Canada Health Division, 1986)

Two types of procedure subsets were constructed. The first was an 'ever' group where women must have had the procedure of interest, but may have had others, in any time sequence, within the study period. This group was constructed primarily to maximize statistical power because of the greater number of expected events. As well, person-years were calculated from the procedure of interest. The second was an 'only' group where the type of procedure being examined was the only one experienced by the women in the study period. An example of the difference in power is very clear for colon cancer in women who had a unilateral oophorectomy. To detect a RR=1.5, with alpha (2-tailed)=0.05, power is 89% for women who ever had the procedure, and 45% for women who only had the procedure (Breslow et al., 1987; Hsieh, 1991). This 'only' group was constructed to simplify the interpretation of the results. It is possible, however, that a women may have had procedures before the study period; this could not be taken into consideration.

Certain procedures were recoded to properly indicate the type of surgery experienced by a woman. Specifically, women who had a hysterectomy plus a bilateral salpingo-oophorectomy were

simultaneously coded as having had a hysterectomy (8030-8060) and a bilateral salpingo-ovariectomy (7751). These codes had to be merged as a new unique code to indicate the complete procedure. Women who had a hysterectomy and subsequent oophorectomy had to be identified. The procedures rarely occurred on the same date, so women who had the oophorectomy within six months of the first procedure were given the new code indicating that the two procedures had occurred close together in time. Ninety-four percent had the second procedure within one month of the first and 94.5% within six months. The date of entry into the cohort was defined as the second procedure date to give fewer person-years and thus a conservative estimate of the expected number of events. Approximately 52,658 women were given the new procedure code, the exact number depending upon the specific cohort being examined. This was also done for salpingectomy associated with the removal of an ectopic fetus (7852) which could also have the simultaneous removal of the single ovary (7720). At six months only 3.6% received a new code because of the small number of this actual combination. Other combinations were examined as possibly requiring recoding due to potential misclassification, however these were discounted due to the extremely small number of records involved. For example, perhaps bilateral oophorectomy (7741) may have been simultaneously coded with hysterectomy rather than the proper bilateral salpingo-oophorectomy (7751).

Outcome Definition

Cancer cases were identified through the Ontario Cancer Registry (OCR). They included residents of Ontario who had been diagnosed from the beginning of the study (April 1979) to December 31, 1993 with a primary cancer of the stomach, colon or rectum. This could have been

a first or a second primary cancer. In the event that a woman had two relevant primary cancer diagnoses, person-years were calculated to the first event and then from the first event to the second. The OCR takes both primary events into consideration when calculating incidence rates, therefore both events had to be observed for a fair comparison. Also, if person-years were accumulated from the surgery to the first event and from surgery to the second event, then this would increase the person-years. Thus, the expected number of events would increase thereby reducing the relative risk estimates. This would cause them to be less conservative than possible. The expected number of cancer events was estimated by using an external comparison group: Ontario females, standardized for age and calendar year with the study cohort.

Table 1.2 describes the cancer outcomes, by site and ICD-9 code (World Health Organization, 1977), evaluated in this study.

Table 1.2 Cancer Outcomes Listed by Site and Assigned ICD-9 Code*

Cancer Site	**ICD-9 Code**
Stomach	151.0-151.9
Colon	153.0-153.9
Rectum	154.0-154.9
Colorectal	153.0-154.9
Proximal Colorectal	153.0, 153.1, 153.4-153.7
Distal Colorectal	153.2, 153.3, 154.0-154.2

*International Classification of Diseases, Injuries and Causes of Death- Nineth Code (World Health Organization, 1977)

Analysis

The procedure subsets were created using the Statistical Analysis System (SAS Institute Inc.,

1988). Descriptive statistics were calculated for the variables age and time since the procedure. The groups were then analyzed using a person-years calculation (Coleman et al., 1989). The accumulation of person-years began at the time of the surgical procedure and continued until the endpoint of death, a relevant cancer event, or the end of the study period on December 31, 1993, except in the event of a second primary event where the person-years were accumulated from the first to the second event. The OCR provided the incidence rates/100,000 women which were used in determining the expected number of events. These rates were stratified by five-year age groups and by one-year calendar periods. As well, they were site-specific and, in the case of the subsite analysis, subsite-specific.

The first analysis compared the observed and the expected numbers of stomach, colon, rectal, colorectal cancer, as well as the subgroups of colorectal cancer, proximal and distal (excluding uncertain or unknown subsites). The analysis then focused on stratifying the groups by age at procedure (15-36, 37-49, 50-64 years of age) and by time since the procedure (0.5-1.9, 2-4.9, 5-15 yrs) individually and then in combination (age and follow-up time). Stratification was only possible if there were sufficient cancer events. Age groups were created to stratify for endogenous hormonal exposure. Two premenopausal groups were created (15-36, 37-49) to detect differences in women with varying lifetime exposures to endogenous hormones. As well, a postmenopausal group (50-64) was created. The groups formed by these stratification criteria were mutually exclusive. Time since the procedure was stratified to explore a variety of lengths of follow-up. This stratification was determined in part by the distribution of cancer events. The stratum 0.5-1.9 years, however, was created to help observe possible detection bias, while the strata of 2-4.9 years and 5-15 years could be used as comparison and to explore trends in cancer risk. The time groups were not mutually exclusive in that person-years were assigned to the appropriate time strata. For example, if a women

was followed for four years, person-years would be in the strata 0.5-1.9 years and 2-4.9 years.

To incorporate the variability associated with a relative risk point estimate, 95% confidence intervals were calculated using the Byar approximation (Breslow et al., 1987). Chi-square statistics were used to evaluate interaction and trend where appropriate (Breslow et al., 1987).

RESULTS

DESCRIPTIVE STATISTICS

Subgroup characteristics do not greatly vary between the different cancer outcome cohorts. Tables 2.1-2.6 describe the mean age (years) and mean time (years) since the procedure of interest until the end of the study. Median values were calculated, but are not reported because they are either the same or very similar to the reported mean values. Both types of subgroups are described: those women who 'ever' had a procedure, and those who 'only' had the procedure of interest. What is apparent is how mean age differs by the type of surgical procedure. For example, older women tend to have a hysterectomy whereas younger women tend to have tubal sterilization. Time from the procedure until the end of the follow-up period is similar for all subgroups.

Table 2.1 Mean Age at Procedure, Time (years) Since Procedure and Standard Deviation for Cohort Examined for **Stomach** Cancer - 'Ever' and 'Only' Had a Procedure

Subgroup		N	Mean Age(sd)	Mean Time(sd)
Unilateral Oophorectomy	-ever	67751	38.4(9.2)	7.8(4.1)
	-only	22490	36.0(11.0)	6.9(3.9)
Unilateral Tubal Sterilization	-ever	28284	31.6(7.2)	7.3(4.0)
	-only	17451	30.0(6.4)	6.9(3.9)
Bilateral Tubal Sterilization	-ever	274155	32.3(5.7)	7.6(4.4)
	-only	239376	32.3(5.6)	7.3(4.4)
Hysterectomy	-ever	188046	40.6(8.4)	7.7(4.0)
	-only	122895	41.4(8.6)	7.8(4.1)
Hysterectomy plus	-ever	78011	47.5(8.3)	7.4(4.1)
Bilateral Salpingo-oophorectomy	-only	74140	47.9(8.2)	7.4(4.1)

Table 2.2 Mean Age at Procedure, Time (years) Since Procedure and Standard Deviation for Cohort Examined for **Colon** Cancer - 'Ever' and 'Only' Had a Procedure

Subgroup		N	Mean Age(sd)	Mean Time(sd)
Unilateral Oophorectomy	-ever	67485	38.4(9.2)	7.8(4.0)
	-only	22278	35.9(10.9)	7.6(4.1)
Unilateral Tubal Sterilization	-ever	28258	31.6(7.2)	7.3(4.0)
	-only	17442	29.8(6.4)	6.9(3.9)
Bilateral Tubal Sterilization	-ever	274127	32.3(5.7)	7.6(4.4)
	-only	239368	32.3(5.5)	7.3(4.4)
Hysterectomy	-ever	187923	40.6(8.4)	7.7(4.0)
	-only	122849	41.4(8.6)	7.8(4.1)
Hysterectomy plus Bilateral Salpingo-oophorectomy	-ever	77789	47.5(8.3)	7.4(4.1)
	-only	73933	47.9(8.1)	7.4(4.1)

Table 2.3 Mean Age at Procedure, Time (years) Since Procedure and Standard Deviation for Cohort Examined for **Rectal** Cancer -'Ever' and 'Only' Had a Procedure

Subgroup		N	Mean Age(sd)	Mean Time(sd)
Unilateral Oophorectomy	-ever	67644	38.4(9.2)	7.8(4.1)
	-only	22414	35.9(11.0)	7.6(4.1)
Unilateral Tubal Sterilization	-ever	28277	31.6(7.2)	7.3(4.0)
	-only	17446	29.8(6.4)	6.9(3.9)
Bilateral Tubal Sterilization	-ever	274138	32.3(5.7)	7.6(4.4)
	-only	239368	32.3(5.6)	7.3(4.4)
Hysterectomy	-ever	187976	40.6(8.4)	7.4(4.0)
	-only	122863	41.4(8.6)	7.8(4.1)
Hysterectomy plus Bilateral Salpingo-oophorectomy	-ever	77916	47.5(8.3)	7.4(4.1)
	-only	74053	47.9(8.2)	7.4(4.1)

Table 2.4 Mean Age at Procedure, Time (years) Since Procedure and Standard Deviation for Cohort Examined for **Colorectal** Cancer -'Ever' and 'Only' Had a Procedure

Subgroup		N	Mean Age(sd)	Mean Time(sd)
Unilateral Oophorectomy	-ever	67366	38.3(9.2)	7.8(4.0)
	-only	22142	35.8(10.9)	7.6(4.1)
Unilateral Tubal Sterilization	-ever	28252	31.5(7.2)	7.3(4.0)
	-only	17438	29.8(6.4)	6.9(3.9)
Bilateral Tubal Sterilization	-ever	274106	32.3(5.7)	7.6(4.4)
	-only	239360	32.3(5.6)	7.3(4.4)
Hysterectomy	-ever	187838	40.6(8.4)	7.7(4.0)
	-only	122810	41.4(8.6)	7.8(4.1)
Hysterectomy plus Bilateral Salpingo-oophorectomy	-ever	77676	47.5(8.3)	7.4(4.1)
	-only	73828	47.9(8.1)	7.4(4.1)

Table 2.5 Mean Age at Procedure, Time (years) Since Procedure and Standard Deviation for Cohort Examined for **Proximal Colorectal** Cancer - 'Ever' and 'Only' Had a Procedure

Subgroup		N	Mean Age(sd)	Mean Time(sd)
Unilateral Oophorectomy	-ever	67686	38.4(9.2)	7.8(4.1)
	-only	22440	36.0(11.0)	7.6(4.1)
Unilateral Tubal Sterilization	-ever	28275	31.6(7.2)	7.3(4.0)
	-only	17448	29.9(6.4)	6.9(3.9)
Bilateral Tubal Sterilization	-ever	274146	32.3(5.7)	7.6(4.4)
	-only	239374	32.3(5.6)	7.3(4.4)
Hysterectomy	-ever	188016	40.6(8.4)	7.4(4.0)
	-only	122887	41.4(8.6)	7.8(4.1)
Hysterectomy plus Bilateral Salpingo-oophorectomy	-ever	77930	47.5(8.3)	7.4(4.1)
	-only	74064	47.9(8.2)	7.4(4.1)

Table 2.6 Mean Age at Procedure, Time (years) Since Procedure and Standard Deviation for Cohort Examined for **Distal Colorectal** Cancer -'Ever' and 'Only' Had a Procedure

Subgroup		N	Mean Age(sd)	Mean Time(sd)
Unilateral Oophorectomy	-ever	67511	38.4(9.2)	7.8(4.0)
	-only	22305	35.9(10.9)	7.5(4.1)
Unilateral Tubal Sterilization	-ever	28265	31.6(7.2)	7.3(4.0)
	-only	17442	29.8(6.4)	6.9(3.9)
Bilateral Tubal Sterilization	-ever	274125	32.3(5.7)	7.6(4.4)
	-only	239366	32.3(5.6)	7.3(4.4)
Hysterectomy	-ever	187925	40.6(8.4)	7.7 (4.0)
	-only	122848	41.4(8.6)	7.8(4.1)
Hysterectomy plus Bilateral Salpingo-oophorectomy	-ever	77815	47.5(8.3)	7.4(4.1)
	-only	73959	47.9(8.1)	7.4(4.1)

PERSON-YEARS ANALYSIS

Overall Analysis

The overall relative risk estimates for the different cancer outcomes generally indicate a protective effect of the procedures considered and often the effects are statistically significant (see Tables 2.7-2.12). Women who underwent any of the procedures have point estimates for stomach cancer consistently below 1 (Table 2.7), most of these being statistically significant with the exemption women who **ever** and **only** had a unilateral tubal sterilization and **only** a unilateral oophorectomy.

There are consistent protective effects for colon cancer associated with the gynecological surgical procedures as indicated by the overall relative risk estimates (Table 2.8). Women who had a bilateral tubal sterilization, hysterectomy, or hysterectomy plus bilateral salpingo-oophorectomy (BSO) have significantly protective relative risk estimates. Those who had the other procedures may

have relative risk point estimates that are protective, but are not statistically significant.

The overall relative risk estimates of rectal cancer are not consistently protective (Table 2.9). Interestingly, women who ever had a unilateral oophorectomy (RR=1.07, 95% CI= .81-1.44) and those who only had the procedure (RR=1.68, 95% CI=.05-2.54) have elevated risk estimates, but neither are statistically significant. The other procedures yielded point estimates that indicate a protective effect. Women who only had a hysterectomy have a significantly reduced relative risk estimate. As well, women who had a hysterectomy plus BSO also experienced a significantly protective effect, despite whether they ever had the surgery or only had it.

The relative risk estimates for colorectal cancer (Table 2.10) indicate a protection associated with having a bilateral tubal sterilization, a hysterectomy or a hysterectomy plus BSO. Otherwise the other procedures have risk estimates less than one which are not statistically significant. Women who only had a unilateral oophorectomy had a relative risk estimate that is somewhat elevated, however this is not significant.

Table 2.11 indicates the consistent protective effects for proximal colorectal cancer associated with all of the procedures. Statistically significantly reduced relative risk estimates are observed for women who had a bilateral tubal sterilization or a hysterectomy plus BSO. Although the other results are not statistically significant, the 95% confidence intervals show that they are of borderline significance.

Reduced risk of distal colorectal cancer is associated with some of the procedures examined (Table 2.12). Hysterectomy and hysterectomy plus BSO are associated with protective relative risks, as well as women who ever had a unilateral oophorectomy. The other procedures examined had risk estimates that were less than one, but not significantly so.

Table 2.7 Stomach Cancer Overall Relative Risk Estimates and 95% Confidence Intervals (CI)- 'Ever' and 'Only' Had a Procedure

	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
Unilateral Oophorectomy					
ever	67751	537866.0	16	26.2	0.61(0.35-0.99)
only	22490	170001.4	5	7.8	0.64(0.21-1.48)
Unilateral Tubal Sterilization					
ever	28284	206768.8	3	4.8	0.62(0.13-1.79)
only	17451	120226.5	2	2.1	0.95(0.11-3.32)
Bilateral Tubal Sterilization					
ever	274155	2081467.0	29	48.6	0.60(0.40-0.86)
only	239376	1753041.0	24	39.9	0.60(0.39-0.90)
Hysterectomy					
ever	188046	1455521.0	48	89.6	0.54(0.40-0.71)
only	122895	962958.3	35	64.7	0.54(0.38-0.75)
Hysterectomy plus bilateral salpingo-oophorectomy					
ever	78011	573026.1	42	60.4	0.70(0.50-0.94)
only	74140	551333.8	42	59.3	0.71(0.51-0.96)

Table 2.8 Colon Cancer Overall Relative Risk Estimates and 95% Confidence Intervals (CI)- 'Ever' and 'Only' Had a Procedure

	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
Unilateral Oophorectomy					
ever	67485	536458.5	102	108.3	0.940(.77-1.14)
only	22278	169020.5	29	32.2	0.87(0.58-1.25)
Unilateral Tubal Sterilization					
ever	28258	206630.7	13	17.7	0.73(0.39-1.25)
only	17442	120192.8	4	7.2	0.55(0.15-1.40)
Bilateral Tubal Sterilization					
ever	274127	2080861.0	132	173.1	0.76(0.64-0.90)
only	239368	1752647.0	107	140.8	0.76(0.62-0.92)
Hysterectomy					
ever	187923	1454003.0	339	381.9	0.89(0.80-0.99)
only	122849	962113.0	236	278.7	0.85(0.74-0.96)
Hysterectomy plus Bilateral Salpingo-oophorectomy					
ever	77789	571492.1	243	278.3	0.87(0.77-0.99)
only	73933	549867.8	231	274.2	0.84(0.74-0.96)

Table 2.9 Rectal Cancer Overall Relative Risk Estimates and 95% Confidence Intervals (CI)- 'Ever' and 'Only' Had a Procedure

	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
Unilateral Oophorectomy					
ever	67644	537256.3	49	45.0	1.07(0.81-1.44)
only	22414	169608.1	22	13.1	1.68(0.05-2.54)
Unilateral Tubal Sterilization					
ever	28277	206721.9	6	7.1	0.84(0.31-1.83)
only	17446	120191.4	1	2.8	0.35(0.00-1.78)
Bilateral Tubal Sterilization					
ever	274138	2081225.0	65	69.2	0.94(0.73-1.20)
only	239368	1752874.0	51	56.0	0.91(0.68-1.20)
Hysterectomy					
ever	187976	1454919.0	139	156.1	0.89(0.75-1.05)
only	122863	962587.9	89	113.4	0.79(0.63-0.97)
Hysterectomy plus Bilateral Salpingo-oophorectomy					
ever	77916	572453.9	85	113.1	0.75(0.60-0.93)
only	74053	550791.9	83	111.5	0.75(0.59-0.92)

Table 2.10 Colorectal Cancer Overall Relative Risk Estimates and 95% Confidence Intervals (CI)- 'Ever' and 'Only' Had a Procedure

	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
Unilateral Oophorectomy					
ever	67366	535756.6	151	152.7	0.99(0.84-1.16)
only	22142	168506.8	51	45.3	1.13(0.84-1.48)
Unilateral Tubal Sterilization					
ever	28252	206578.5	19	24.9	0.76(0.46-1.19)
only	17438	120158.4	5	10.1	0.50(0.16-1.15)
Bilateral Tubal Sterilization					
ever	274106	2080552.0	197	243.0	0.81(0.70-0.93)
only	239360	1752463.0	158	197.4	0.80(0.68-0.94)
Hysterectomy					
ever	187838	1453255.0	479	537.9	0.89(0.81-0.97)
only	122810	961671.1	325	392.1	0.83(0.74-0.92)
Hysterectomy plus Bilateral Salpingo-oophorectomy					
ever	77676	570790.8	328	390.7	0.84(0.75-0.94)
only	73828	549197.0	314	385.0	0.82(0.73-0.91)

Table 2.11 Proximal Colorectal Cancer Overall Relative Risk Estimates and 95% Confidence Intervals (CI)- 'Ever' and 'Only' Had a Procedure

	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
Unilateral Oophorectomy					
ever	67686	537523.6	28	39.3	0.710(.47-1.03)
only	22440	169817.0	6	12.4	0.49(0.18-1.05)
Unilateral Tubal Sterilization					
ever	28275	206715.7	2	6.5	0.31(0.04-1.08)
only	insufficient data				
Bilateral Tubal Sterilization					
ever	274146	2081308.0	41	59.7	0.69(0.49-0.93)
only	239374	1752935.0	33	48.5	0.68(0.47-0.96)
Hysterectomy					
ever	188016	1455059.0	126	140.2	0.90(0.75-1.07)
only	122887	962736.4	93	103.5	0.90(0.73-1.10)
Hysterectomy plus Bilateral Salpingo-oophorectomy					
ever	77930	572505.1	79	105.7	0.75(0.59-0.93)
only	74064	550831.5	76	104.3	0.73(0.57-0.91)

Table 2.12 Distal Colorectal Cancer Overall Relative Risk Estimates and 95% Confidence Intervals- 'Ever' and 'Only' Had a Procedure

	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
Unilateral Oophorectomy					
ever	67511	536575.2	67	89.0	0.75(0.58-0.96)
only	22305	169102.3	23	25.6	0.90(0.57-1.35)
Unilateral Tubal Sterilization					
ever	28265	206672.3	10	14.3	0.70(0.34-1.29)
only	17442	120172.4	2	5.6	0.36(0.04-1.24)
Bilateral Tubal Sterilization					
ever	274125	2080915.0	125	141.9	0.88(0.73-1.05)
only	239366	1752695.0	103	115.2	0.89(0.73-1.09)
Hysterectomy					
ever	187925	1454244.0	237	308.7	0.77(0.67-0.87)
only	122848	962233.9	166	223.4	0.74(0.63-0.87)
Hysterectomy plus Bilateral Salpingo-oophorectomy					
ever	77815	571778.3	129	220.1	0.59(0.49-0.70)
only	73959	550152.3	128	216.8	0.59(0.49-0.70)

Age-Stratified Analysis

The age-stratified relative risk estimates describe more specifically what effect is associated with the surgical procedures by providing relative risk estimates for women aged 15-36, 37-49 and 50-64 years at the time of surgery separately. Due to the division of the procedure groups, in some cases age-stratification may not have been possible because of no cancer events occurring in some strata. Tests of interaction were performed to determine if the effect of the procedure is modified by age at procedure. Tests of trend across age groups were performed to evaluate if there is an increase, decrease or no change in effect of procedure as age increases. Appendix II (Tables A2.1-A2.6) contains all age-stratified results. Here, only those situations where there is significant interaction or trend are reported with tables and discussed.

The stratification of certain procedure groups by age for colon cancer is found in Table 2.13. The risk of colon cancer appears to increase with age at procedure for the procedure groups relative to the population. Significant trend statistics exist for women who **only** had a unilateral oophorectomy, those who **ever** and **only** had a hysterectomy however these can be explained by there being relative risk estimates above 1.0 in the stratum of women 50-64, while the first two strata are below one and sometimes protective (as in the case of women who ever and only had a hysterectomy in the age stratum 37-49). This is highlighted in women who **only** had a hysterectomy; there is significant interaction between age and the procedure ($p<0.03$) most likely caused by the much different relative risk in the age stratum 50-64.

Table 2.13 Colon Cancer Age-Stratified Relative Risk Estimates and 95% Confidence Intervals (CI)- 'Ever' and 'Only' Had a Procedure

Unilateral Oophorectomy only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	13212	104689.1	3	4.7	0.63(0.10-1.82)
37-49	6549	47034.8	5	11.3	0.44(0.14-1.02)
50-64	2517	17296.5	21	16.2	1.30(0.80-1.98)
Total	22278	169020.5			

Breslow-Day chi-squared statistic (interaction)= 5.8 (p>0.05) Breslow-Day chi-squared statistic (trend)= 3.9 (p<0.05)

Hysterectomy ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	65522	536949.8	27	37.6	0.72(0.47-1.04)
37-49	99884	7845229.7	152	185.2	0 .82(0.70-0.96)
50-64	22517	171823.1	160	159.1	1.01(0.86-1.17)
Total	187923	1454003.0			

Breslow-Day chi-squared statistic (interaction)= 4.7 (p>0.05) Breslow-Day chi-squared statistic (trend)= 4.5 (p<0.05)

only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	39140	327971.9	19	24.1	0.79(0.48-1.23)
37-49	66005	496856.8	85	124.3	0.68(0.55-0.85)
50-64	17704	137284.4	132	130.3	1.01(0.85-1.20)
Total	122849	962113.0			

Breslow-Day chi-squared statistic (interaction)= 8.4 (p<0.03) Breslow-Day chi-squared statistic (trend)= 5.5 (p<0.03)

The outcome of rectal cancer also yielded some significant results once stratified by age. The effect of procedure varied depending on age at procedure. This result is a significant trend statistic for those who ever had a unilateral oophorectomy due to the significantly elevated relative risk in the oldest age stratum; and those who ever had a hysterectomy possibly due to the risk reduction in the

middle stratum (37-49 years)(see Table 2.14). These trend statistics may also be influenced by the significant interaction that exists between age and the procedure which indicates that there is a separate effect of procedure as age changes for both procedure groups.

Table 2.14 Rectal Cancer Age-Stratified Relative Risk Estimates and 95% Confidence Intervals (CI)- 'Ever' and 'Only' Had a Procedure

Unilateral Oophorectomy
ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	31555	262030.9	6	5.5	1.10(0.40-2.37)
37-49	30561	234810.4	18	25.9	0.69(0.41-1.10)
50-64	5528	40414.9	25	13.7	1.83(1.18-2.70)
Total	67644	537256.3			

Breslow-Day chi-squared statistic (interaction)= 10.6 ($p<0.01$) Breslow-Day chi-squared statistic (trend)= 5.3 ($p<0.03$)

Hysterectomy
ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	65523	536981.6	18	13.2	1.37(0.81-2.16)
37-49	99917	745753.5	64	81.4	0.79(0.61-1.00)
50-64	22536	172183.5	58	61.5	0.94(0.72-1.22)
Total	187976	1454919.0			

Breslow-Day chi-squared statistic (interaction)= 8.0 ($p<0.03$) Breslow-Day chi-squared statistic (trend)= 6.4 ($p<0.03$)

Table 2.15 shows results of age-stratification for colorectal cancer. Significant age at procedure trend is observed for women who ever had a unilateral oophorectomy. This colorectal cancer risk increasing with age is due to the significantly increased risk for women 50-64 years at the time of procedure. Significant interaction ($p<0.03$) between unilateral oophorectomy and age shows an age-specific effect of the procedure. As well, women who ever had a hysterectomy have

significant interaction between the procedure and age ($p<0.03$).

Table 2.15 Colorectal Cancer Age-Stratified Relative Risk Estimates and 95% Confidence Intervals (CI)- 'Ever' and 'Only' Had a Procedure

Unilateral Oophorectomy ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	31542	261947.8	17	20.6	0.82(0.48-1.32)
37-49	30481	234255.2	70	84.2	0.83(0.65-1.05)
50-64	5343	39553.7	64	47.8	1.34(1.03-1.71)
Total	67366	535756.6			

Breslow-Day chi-squared statistic (interaction)= 8.6 ($p<0.03$) Breslow-Day chi-squared statistic (trend)= 6.4 ($p<0.03$)

Hysterectomy only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	39135	327903.0	29	32.6	0.89(0.60-1.28)
37-49	65997	496744.6	124	179.2	0.69(0.58-0.83)
50-64	17678	137023.4	172	180.3	0.95(0.82-1.11)
Total	122810	961671.1			

Breslow-Day chi-squared statistic (interaction)= 7.6 ($p<0.03$) Breslow-Day chi-squared statistic (trend)= 3.3 ($p>0.05$)

Time-Stratified Analysis

The cohort was stratified to yield stratum-specific relative risk estimates for time since the procedure. Not all procedure groups could be stratified for some of the cancer outcomes because of a dearth of events. Tests of interaction were performed to detect a significant effect of procedure with age. As well, tests of trend across time groups were performed to evaluate if there is an increase, decrease or no change in the effect of the procedure as time from the procedure increases.

Time-stratified tables for all procedure groups and cancer outcomes are found in Appendix II (Tables A2.7-A2.12). Reported below are only those tables where there is significant interaction between the procedure and time or trend in cancer risk as time from procedure lengthens.

The association of the gynecological procedures and colon cancer, once stratified for time since the procedure, is quite varied (see Table 2.17). Significant statistical trend for risk of cancer is also observed over the time strata. There is an effect of time since procedure on trend with greater time since procedure decreasing trend. This is because of the significantly elevated risk in the time period 0.5-1.9 years and the point estimates below 1.0 in the next two strata which are similar in value for women who **ever** had a unilateral oophorectomy and **only** had a unilateral oophorectomy. This is also true for those who **ever** had a unilateral tubal sterilization. Women who **ever** had a bilateral tubal sterilization had significant trend likely due to the protective effect in the stratum 5-15 years. As well, for all the procedure groups with significant trend, significant interaction was detected further supporting that although statistical trend was detected the difference of effect of procedure by time was influential. This significant interaction of time and the procedure is observed in the case of women who **ever** had a unilateral oophorectomy ($p<0.01$); those who **only** had a unilateral oophorectomy ($p<0.01$); those who **ever** had a unilateral tubal sterilization ($p<0.01$); and women who **ever** had a bilateral tubal sterilization ($p<0.05$).

Table 2.17 Colon Cancer Time-Stratified Relative Risk Estimates and 95% Confidence Intervals (CI)- 'Ever' and 'Only' Had a Procedure

Unilateral Oophorectomy

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	67485	131462.3	28	16.7	1.67(1.11-2.42)
2-4.9	61857	165442.9	20	27.2	0.73(0.45-1.13)
5-15	48587	239553.2	54	64.3	0.84(0.63-1.10)
Total	67485	536458.5			

Breslow-Day chi-squared statistic (interaction)= 11.5($p<0.01$) Breslow-Day chi-squared statistic (trend)= 6.3 ($p<0.03$)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	22278	43101.0	13	5.7	2.29(1.22-3.90)
2-4.9	20024	52411.2	5	8.4	0.59(0.19-1.37)
5-15	15080	73508.2	11	18.1	0.61(0.30-1.08)
Total	22278	169020.5			

Breslow-Day chi-squared statistic (interaction)=14.7 ($p<0.01$) Breslow-Day chi-squared statistic (trend)= 10.2 ($p<0.01$)

Unilateral Tubal Sterilization

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	28258	54785.9	7	2.7	2.64(1.06-5.42)
2-4.9	25469	66243.1	1	4.4	0.23(0.00-1.14)
5-15	18784	85601.7	5	10.7	0.47(0.15-1.09)
Total	28258	206630.7			

Breslow-Day chi-squared statistic (interaction)= 15.8 ($p<0.01$) Breslow-Day chi-squared statistic (trend)= 8.7 ($p<0.01$)

Bilateral Tubal Sterilization ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	274127	526866.9	16	21.7	0.74(0.42-1.20)
2-4.9	239464	604356.0	36	35.3	1.02(0.72-1.41)
5-15	176135	949638.4	80	116.1	0.69(0.55-0.86)
Total	274127	2080861.0			

Breslow-Day chi-squared statistic (interaction)= 7.2 ($p<0.05$) Breslow-Day chi-squared statistic (trend)= 7.2 ($p<0.01$)

A variety of associations for the surgical procedures and colorectal cancer are observed (Table 2.18). Women who **ever** and **only** had a unilateral oophorectomy have a significant interaction of time and procedure ($p<0.01$) as well as significant positive trend with an increase in time since the procedure decreasing risk due to a significant elevation in cancer risk within 0.5-1.9 years of time since the procedure and the reduced risk estimated for the remaining time strata. This is also true of women who **ever** had a unilateral tubal sterilization in that significant interaction is observed ($p<0.01$) as well as statistically significant trend of decreasing risk with time from procedure.

Table 2.18 Colorectal Cancer Time-Stratified Relative Risk Estimates and 95% Confidence Interval (CI)- 'Ever' and 'Only' Had a Procedure

Unilateral Oophorectomy

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	67366	131250.5	40	24.4	1.64(1.17-2.24)
2-4.9	61771	165248.9	34	39.3	0.86(0.60-1.21)
5-15	48534	239257.3	77	89.0	0.87(0.68-1.08)
Total	67366	535756.6			

Breslow-Day chi-squared statistic (interaction)= 12.5 (p<0.01) Breslow-Day chi-squared statistic (trend)= 8.5 (p<0.01)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	22142	43101.0	18	8.3	2.18(1.29-3.45)
2-4.9	19849	52411.2	11	12.1	0.91(0.45-1.63)
5-15	14948	73508.2	22	25.0	0.88(0.55-1.33)
Total	22142	168506.8			

Breslow-Day chi-squared statistic (interaction)= 10.0 (p<0.01) Breslow-Day chi-squared statistic (trend)= 7.2 (p<0.01)

Unilateral Tubal Sterilization

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	28252	54776.3	9	3.9	2.30(1.05-4.36)
2-4.9	25465	66231.1	1	6.4	0.16(0.00-0.79)
5-15	18780	85571.1	9	14.5	0.62(0.28-1.17)
Total	28252	206578.5			

Breslow-Day chi-squared statistic (interaction)= 15.6 (p<0.01) Breslow-Day chi-squared statistic (trend)= 6.2 (p<0.03)

Table 2.19 describes the stratified relative risk estimates for distal colorectal cancer where test of trend is significant. Tests for interaction are not significant however statistically significant trend is observed for women who **ever** and **only** had a hysterectomy plus BSO. There appears to be increasing risk as time since procedure increases.

Table 2.19 Distal Colorectal Cancer Time-Stratified Relative Risk Estimates and 95% Confidence Intervals (CI)- 'Ever' and 'Only' Had a Procedure

Hysterectomy plus Bilateral Salpingo-oophorectomy

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	77815	150220.4	16	43.5	0.37(0.21-0.60)
2-4.9	69337	180116.5	37	62.5	0.59(0.42-0.82)
5-15	51322	241441.4	76	114.1	0.67(0.53-0.83)
Total	77815	571778.3			

Breslow-Day chi-squared statistic (interaction)= 4.7 (p>0.05) Breslow-Day chi-squared statistic (trend)= 4.4 (p<0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	73959	142966.1	16	42.6	0.38(0.22-0.61)
2-4.9	66175	172486.7	36	61.4	0.59(0.41-0.81)
5-15	49348	234699.5	76	112.8	0.67(0.53-084)
Total	73959	550152.3			

Breslow-Day chi-squared statistic (interaction)= 4.7 (p>0.05) Breslow-Day chi-squared statistic (trend)= 4.4 (p<0.05)

DISCUSSION

This study was conducted to evaluate the relationship between certain common gynecological surgical procedures and the risk of stomach, colon, and rectal cancers. The data were provided by a large, population-based, historical cohort study (Kreiger et al., 1997). Generally, the results demonstrated protective associations between the procedures and cancer, although this was not true in all circumstances.

Stomach Cancer

Examination of the results of stomach cancer risk allows for certain comparisons with the literature. The first is that risk reductions were observed for all of the procedures in the overall analysis. This was not anticipated as the epidemiologic literature suggests that there is an inverse relationship of fertile life and stomach cancer risk, specifically, that endogenous estrogen exposure is protective (La Vecchia et al., 1994; Palli et al., 1994). Thus, the truncation of exposure could lead to an increase in risk for stomach cancer. The basic laboratory work shows that there are estrogen receptors (ER) in the stomach (Tokunaga et al., 1983; Sica et al., 1984), although the role they play is unknown. Survival may be influenced by hormones and the presence of ER, but the epidemiologic evidence perhaps indicates that estrogen may inhibit cancer from even forming. Perhaps once cancer cells appear, they behave differently in the presence of hormones compared to the normal gastric mucosa.

It was expected that there might be some variation in the relative risk outcomes between the

different types of procedure groups. This is due to the different potential for tissue damage and subsequent hormone (estrogen) reduction of the different types of procedures, not taking into consideration unmeasured other estrogen exposure, either endogenous or exogenous. For example, the literature (Cattanach, 1985) suggests that tubal sterilization is most disruptive to the blood supply to the ovary whereas hysterectomy would be less so. Obviously, a hysterectomy plus bilateral salpingo-oophorectomy (BSO) would have the greatest impact on estrogen levels since the ovarian hormone source is entirely removed. On the other hand, unilateral tubal sterilization and unilateral oophorectomy should have the least effect.

The overall analysisis not stratified by age and time because of too few cancer events, nor are potential confounders considered, making the resulting tables difficult to interpret. If a hormonal influence on the risk of stomach cancer exists, then it is unlikely that women who had a unilateral tubal sterilization should have the protective risk estimates observed. This is because damage to one fallopian tube and ovarian artery may truncate the hormone output of the associated ovary in time; in that event, the second ovary should begin to function optimally if it is not already doing so. Hence there should be no hormonal related change in risk for stomach cancer. The results for women who had a unilateral tubal sterilization while not statistically significant, are more difficult to interpret, as the risk estimates are below one. The fact that women who only had this procedure have a risk estimate of 1.0 may indicate that there is no change in risk as expected. Women who had a unilateral oophorectomy were expected not to be influenced in the long term. Estrogen output may have been reduced in the short term (a few months) due to the requirement of the other ovary, and the time required for it to begin to function at maximum. Thus, the protective effect observed for those who ever or only had the procedure was unexpected.

Hysterectomy plus BSO was expected to be of greatest influence to the hormone supply, not considering exogenous hormone use. Women were typically older at this procedure, though, and therefore would have had a longer lifetime exposure to endogenous hormones, so we might not expect a decrease in risk. The statistically significant protective effect for those who had a bilateral tubal sterilization and hysterectomy was opposite to what was expected. It is fitting however that these results are similar because of the similarity in effect to the ovarian artery which may suggest similar hormonal changes or something else in common to the women in the bilateral tubal sterilization and hysterectomy procedure groups. The descriptive statistics for age at procedure show that women in these procedure groups may choose to have the tubal sterilization or hysterectomy at different ages thereby changing lifetime exposure, however the ranges overlap.

Stratification by age shows there was no significant trends of effect of procedure with age for any of the procedures. This was not expected for the procedures of bilateral tubal sterlization, hysterectomy and hysterectomy plus BSO given the literature showing an inverse relationship between endogenous estrogen exposure and stomach cancer risk (LaVecchia et al., 1994; Palli et al., 1994). The expectation was that the lower the age at procedure, the greater the risk of stomach cancer since hormone level change would occur at a younger age and have a longer time to affect the system. A control group (i.e. unilateral tubal sterilization group), which would have aided in the interpretation, does not exist to compare with the other procedure groups. As well, assessment of these stratified results is difficult due to the variability associated with the estimates and how they overlap. The lack of trends however, is indicative that a hormonal explanation is not appropriate.

The time-stratified analyses were done because the literature gave some indication that some time might be necessary for hormonal changes to manifest after some of the procedures (Cattanach,

1985; Siddle, 1987), hence women with the shortest follow-up were expected to have a lower risk than those with longer follow-up. None of the trends was significant, providing evidence that the observed reductions are not due to the associated procedures. This was expected to some degree for all the procedures with those having had the unilateral oophorectomy being the least affected, if at all, perhaps only in the first stratum due to the possible requirement of the retained ovary to function properly. What is noticeable is that those who had a hysterectomy plus BSO experienced no change. This may be due to age not being taken into consideration in a stratified manner, as many of the women tend to be nearer the age of menopause.

It was expected that there be some variation in impact of procedures on ovarian function. The consistently significantly reduced relative risks observed for stomach cancer may show that despite the absolute potential for hormone truncation due to gynecological procedures only, risk can be altered. The overall protective trend of these gynecological procedures on stomach cancer may be influenced by confounding factors. Given the information about who might have the procedures and the knowledge of the cancers, certain variables can be identified as possibly being associated with having the procedure and cancer, however the magnitude of this association may not be clear. These variables are: age, education, income, parity, and exogenous hormone use such as oral contraceptives (OC) and hormone replacement therapy (HRT).

Education and income are positively correlated factors and can be discussed together. This understanding is derived from the literature that states that stomach cancer is associated with low socioeconomic status, based on income, education, occupation or census tract information (Schottenfeld et al., 1996). Women of lower SES may tend to have a hysterectomy (Koepsell et al., 1980). Women with stomach cancer tend to be of lower SES therefore unadjusted analyses would

increase the relative risk estimates for those in the hysterectomy and hysterectomy plus BSO procedure groups. Perhaps in the case of contraceptive procedures like tubal sterilization, the relative risk might be brought closer to 1.0 as women may be more likely to be of higher SES. However, given the general reduction in risk for all procedure groups, SES may not be an important factor assuming that the SES profile of women differs depending on their type of gynecological surgery. If the SES profiles are similar to the women of different procedure groups (hysterectomy vs. bilateral tubal sterilization) then one could speculate that SES may be responsible for lowering the relative risk estimates as observed.

When considering stomach cancer and endogenous hormones and exogenous hormone use, the literature is limited. It has been suggested that parity and oral contraceptive use increase risk (LaVecchia et al., 1994; Palli et al., 1994). Further they could alter the risk since women who have these procedures are more inclined to be parous and to use oral contraceptives (Kuh et al.,1995; Santow et al.,1992). Women who have these procedures, however, may be more parous which might result in the relative risk estimates being inflated (Koepsell et al., 1980). Separate examination and comparison of the procedure groups does not provide insight into the amount of possible influence of parity or oral contraceptive use because of how variable the women in the groups are. The long-term effect of these factors and their influence on older women is also not understood. Oral contraceptives may be more widely used in the younger cohort members. However, the composition of oral contraceptives has changed over time making comparisons of women within the cohort procedure groups difficulat. Hormone replacement therapy is not well understood but it is associated with a decrease in risk of stomach cancer (LaVecchia et al., 1994; Palli et al., 1994) thus it would contribute to the reduction in risk observed especially for the women observed to be protected in the

age statum 50-64 years as they would be more inclined to use it. It is difficult to know how HRT might affect the estimates because it is not known if it is related to the surgical procedures, and if it is, how strongly. One exception may be that women who have had a hysterectomy plus bilateral salpingo-oophorectomy may be more inclined to use HRT because of the complete removal of the ovarian hormone source.

Colon and Rectal Cancers

The expectation for colon and rectal cancers was that some of the procedures would reduce cancer risk. This is based on the literature that points to the relationship between endogenous hormones and risk of colorectal cancer due to changes in bile acids (McMichael et al., 1980). As well, risk may be decreased as seen in the laboratory evidence which more strongly suggests that estrogen exposure is positively linked to cancer risk by means of estrogen receptors (Singh et al., 1994, Ziv et al., 1994). Although the epidemiologic evidence is less suggestive of a hormonal influence (Franceschi et al., 1991), a risk decrease was expected for some of the procedures that would have caused eventual hormone reduction, such as a bilateral tubal sterilization, through ovarian tissue necrosis (Cattanach, 1985).

The overall relative risks vary with each procedure and specific cancer outcome of interest. In general, the expectation was met that risk should be reduced for women who had a bilateral tubal sterilization, hysterectomy and hysterectomy plus BSO. Cattanach (1985) suggested that tubal sterilization and hysterectomy could damage the ovarian artery, which would cause decreased flow of blood into the ovary, causing tissue damage and diminution of hormone production. Hysterectomy plus BSO would simply be a more sudden decline in endogenous estrogen due to the complete

elimination of ovarian hormone production.

Women who had a unilateral tubal sterilization did not have a significant risk reduction. The point estimate is suggestive that this procedure may be associated with a protective effect, even though this was not hypothesized. The unilateral tubal sterilization group was created to compare with the other results because it was not expected to have an effect on cancer risk. This provides some reason to suspect that risk reduction seen for bilateral tubal sterilization, hysterectomy and hysterectomy plus BSO may have to do with a factor associated with the procedures and common to the women who have them, but may not be the procedures themselves.

The overall estimates do not take into consideration age at the procedure and the length of time from the procedure which could both influence the results. That women who had a hysterectomy plus BSO or who had a bilateral tubal sterilization had relative risk estimates which are significantly protective makes a hormonal explanation questionable since age at the procedure for women who had a hysterectomy plus BSO was on average 48 years of age while those who had a bilateral tubal sterilization were on average 32 years of age at the time of the procedure. This implies different lifetime exposures to estrogen. The mean follow-up time from the procedures may be similar, however, in conjunction with age, the lifetime exposure of endogenous hormones would be more variable.

Age-stratification was performed to provide further support for the hormonal hypothesis. The younger the age at truncation of estrogen, the greater the benefit. A positive trend was expected (i.e., as age increases, cancer risk increases) for the procedures that may cause hormonal changes like bilateral tubal sterilization and hysterectomy. For colon cancer, a significant increase in cancer risk with increasing age was observed for women who ever had a hysterectomy and who only had a

hysterectomy, which, given the literature, are consistent with expectations. Also consistent with the literature is the lack of trend observed for women who had unilateral tubal sterilization. A significant trend in risk, however, was observed for women who only had a unilateral oophorectomy which is not consistent with the hormonal theory, and neither is the lack of trend for women who had a bilateral tubal sterilization. This was also the case once rectal cancer risk was examined through age-stratification. Only two groups of women yielded significant trends: those who ever had a unilateral oophorectomy and those who ever had a hysterectomy. Colorectal cancer yielded a significant trend for those who ever had a unilateral oophorectomy and not for the other procedure groups. It should be noted that the significant trend statistics are likely due to the influence of a stratum rather then a real trend.

As well, other sites did not have the pattern of results expected providing evidence that the expected lowering of risk is confounded by one or more unmeasured factors. Perhaps there is no hormonal association. That colon cancer risk behaved more as expected than rectal cancer risk is coherent with the literature in that colon cancer sites would be more greatly affected by bile acids. However, estrogen receptor influence was expected to be the same despite site.

Time-stratification can also be used to test the hypothesis. The longer the time from a procedure that can potentially influence hormone production, the greater the reduction in cancer risk. Inverse trends were expected of some of the procedure groups, however not by those who had a unilateral tubal sterilization or a unilateral oophorectomy because of limited potential hormonal truncation.

As expected women who ever had a bilateral tubal sterilization had a significant trend for colon cancer risk by time. Significant trend was also observed for women who had a unilateral

oophorectomy or a unilateral tubal sterilization, which was not expected. No trend was observed for rectal cancer outcomes. As well, for the outcome of colorectal cancer, unilateral oophorectomy and unilateral tubal sterlization were also significant for trend. These trend statistics, however, may not reflect a true trend but may be influenced by the interaction of time and the procedure. These results for significant trend are puzzling in that they are contradictory to what was hypothesized from the literature. The literature suggests no long-term hormonal variation for unilateral oophorectomy or unilateral tubal sterilization. Perhaps the less invasive procedures, like unilateral tubal sterilization and unilaleral oophorectomy, are associated with a confounding variable responsible for a risk reduction.

The literature provides some evidence that colon cancer risk would be more greatly affected than rectal cancer risk because of changes to the bile acids which would tend to have a greater effect on the colon rather than the rectum. However hormone receptors are most likely equally dispersed throughout the colon and rectum (McMichael et al., 1985) thus the influence of receptors should not vary by anatomic location. For this reason colon and rectal cancers could be examined separately. The overall relative risk estimates, although they may vary, do overlap. Of note is the elevated risk estimate for unilateral oophorectomy for women with rectal cancer, which was not observed for colon cancer risk. To be certain, however, due to the potential misclassification of colon and rectal cancer diagnoses, these sites were also studied together as colorectal cancerl. This just created relative risks that were reflective of combined risk of what was observed for the sites separately, and this did not provide additional insight for the interpretation of the results.

It was expected that proximal colorectal cancer would be more greatly affected than distal colorectal cancer because of the greater opportunity of exposure to bile acids within the proximal

colon than the distal portion (McMichael et al., 1985). Our data do not support this, as the risk estimate confidence intervals overlap substantially.

The results evaluating colon and rectal cancers may be more likely associated with unmeasured factors rather than gynecological procedures and subsequent hormone changes. For the outcomes of colon and rectal cancers the potentially confounding variables are: geographic area of residence (urban/rural), age, education, income, parity, and exogenous hormone use such as oral contraceptives and hormone replacement therapy. Age has already been taken into consideration in the analysis. Each of the other factors can be looked at individually in how it potentially could have altered the risk estimates, however, quantifying the extent of this alteration is difficult.

Women with colon and rectal cancers tend to be of higher SES (Schottenfeld et al., 1996). Therefore unadjusted analyses would decrease the risk estimates, at least for those women who had a hysterectomy, as these women tend to be lower SES (Koepsell et al., 1980). The SES profile of women who had the other types of procedures is not known; therefore the direction of influence is uncertain. Perhaps women who have had a contraceptive procedure such as the bilateral tubal sterilization are of higher SES, thus the relative risk estimates would be inflated. Women in urban environments tend to have an increased risk of hysterectomy as well as an increased risk of colon cancer (Schottenfeld et al., 1996). This relationship might inflate the relative risk estimate since urban women tend to have an elevated risk of hysterectomy (Luoto et al., 1992; Santow et al., 1992). Urban women could not be analysed separately as the data did not identify area of residence. The effects of parity, oral contraceptives and hormone replacement therapy on risk for colon cancer are thought to be protective (McMichael et al., 1985). Thus these might lower the risk estimates if they are also associated with the procedures, such that women who have these procedures are more likely

to be parous and use exogenous hormones (Kuh et al., 1995; Koepsell et al., 1980). It should be noted that the literature shows that the protective effects of parity, oral contraceptives and hormone replacement therapy are often nonsignficant (Potter, 1993), however these may be contributing factors as to why older women, who had a procedure after menopause, have their risk influenced rather than remaining unaffected as would be expected.

Study Limitations and Strengths

There are other limitations to this research that may have had an effect on the results, beyond unmeasured potential confounders such as exogenous hormones (oral contraceptives and hormone replacement therapy), parity, socioeconomic status and geographic area of residence (urban/rural). These can be identified, as well as the strengths of this work, to help understand the results.

This research was dependent on correctly following cohort members through record linkage and the identification of cancer endpoints or death. There is the possibility that records were not linked for two reasons which could have adversely influenced the results: emigration out of Ontario, hence a cancer diagnosis outside the province, and surname change. Not linking women increases the person-years and thus the expected number of events, and would reduce the observed number of events. This would lower the relative risk point estimate. Linkage problems attributed to migration and name changes would be more visible as time since the procedure increases. This is visible in the time-stratified analyses where risk decreases as time increases.

Migration can most likely be discounted as being responsible for risk reduction as time from the procedure increased. Statistics Canada (1993) reports that a very small percentage of women left the province, which differs by age group. On average for a five year period, 3.1% emigrated,

ranging from 1.3% for those 55-64 to 3.5% for women 25-34.

Record linkages are partly dependent upon the surname, hence the concern for name changes. Alternate names were considered. Thus if there was a name change, as in some marriages, then this may have had an effect on the results if the other variables used for linking records were missing or incorrect. It is more likely that younger women marry. In Ontario, the average age for women who marry is 28.8 years, but 25.9 years for first time marriages. Age-specific marriage rates show that women 25-29 have 156.3 marriages/1,000 with this rate showing a gradual decline to 6.3/1,000 for women 60-64. Unfortunately, this does not directly indicate the percentage of name changes for women of different age categories, which makes it difficult to quantify the amount by which the risk estimates could potentially be affected. However, the chance that this would occur in a woman diagnosed with cancer or who died is likely small, given probability of these factors and name change at marriage occuring after gynecological surgery.

Detection bias is another potential limitation of the study which was considered by the study design. Any cancers diagnosed within six months of procedure were excluded. To test if this time period was sufficient, all events diagnosed within a year of a procedure were also excluded. This did not alter the relative risk estimates, but did reduce the number of eligible women. Even though this bias was taken into consideration it may be partly responsible for the trends observed in the time-stratified analyses. The elevated risk estimates from 0.5-1.9 years of follow-up may be attributed to detection bias. Perhaps the surgery raised a health concern that increased medical attention.

Misclassification is also a concern in this study in that disease status may have also been misclassified because linkage was only to cancer events from April 1979 to December 1993. Thus a women may have been diagnosed prior to the start date and included in the cohort. This would

have increased the person-years and therefore reduced the relative risk estimates (having a possible protective effect) by increasing the expected number of events. As well there may have been some misclassification of the exposure because women may have had a relevant procedure prior to April 1979. This then would have underestimated the person-years and expected cancer events. Perhaps they would also be misclassified by procedure group as this first procedure, unaccounted for, would have been different.

In order to have the greatest amount of statistical power, procedure groups were created for women who ever had a procedure, rather than for women who only had a procedure. This is most useful when studying unilateral tubal sterilization and oophorectomy as there sometimes were too few women who only had the procedures versus the number who ever did. Examining a group of women who ever had a procedure makes the results more difficult to interpret because exposure may be misclassified. This is because there may have been a procedure which disrupted ovarian function prior to the one being investigated in the procedure group. To gain an understanding of this potential problem, the average number of procedures per woman was calculated for groups where a procedure was ever performed. Those who had a hysterectomy plus BSO had an average of 1.07 procedures; unilateral or bilateral tubal sterilization, 1.06; hysterectomy 1.18 procedures; and those who had a unilateral oophorectomy had an average of 1.62 procedures. This demonstrates that misclassification exists and influences the amount of time followed per person, and would probably have a different effect for each subgroup. For example, those who had a unilateral oophorectomy may have had other procedures after this surgery, especially given the young average age of this group. It may be that estrogen exposure levels changed, due to subsequent procedures, however the person-years may be accurate. On the other hand, those that had a hysterectomy plus BSO most likely had a procedure

before this indicating that there was some misclassification and a reduced number of person-years measured, thus the expected number of events may be fewer than calculated in the analysis. Also to consider is that a women may have had a procedure that was excluded for study that may have affected hormone output (e.g. fallopian tube repair).

An external comparison group, of Ontario women, was utilized to calculate the expected cancer events for the person-years analysis. An internal comparison group was also considered, consisting of women who were in the preliminary cohort but who were ineligible for the study for reasons other than their ages, such as the type of procedure they had. This group was extremely small (fewer then 75,000) thus statistical power would have been less satisfactory. As well the procedures that were done on these women may have affected them in a way similar to the cohort members, thus the rates may not have been appropriate for comparison. Given these reasons this internal comparison group was not used. Also, the assumption that an internal comparison group could be better matched on potential confounders than the external comparison group may not be valid since women who have procedures for sterilization and those who have other types of procedures for other medical conditions may differ.

The use of the incidence rates derived from the population of women in Ontario during the study period means that the cancer events that occurred within the procedure subgroups of the cohort are also included in the population rates. As a consequence the expected number of events would be increased slightly.

The relative risk estimates are further affected in that second primary cases of stomach, colon and rectal cancer were also included as observed events and person years counted until this second event. This was done because both first and second primary cases are included in the population rates

by the OCR and therefore were used to create the expected number of events in the person-years analysis. Although risk for a second cancer event may change after a first, these specific rates were not available. Also, second primary cancers were included despite the type of primary event. This strategy increases the person-years slightly. The average percentage of second primary cases in these cohorts is quite small at less than 5%, hence this is not a significant problem.

Outpatient records were only included after April 1990, and women who had outpatient surgery may be different, potentially confounding the results. A small analysis was performed excluding all records of surgery performed after 1989 and the relative risk estimates were either identical or extremely similar. This shows that these women did not cause any difference to the results.

When examining several types of gynecological surgery in relation to several types of cancer, there is the problem of multiple comparisons where, by chance alone, there may be a significant result. The findings of this study have been considered in light of the information presented in previous studies. In some instances significant results were not related to prior hypotheses. These, as well as the nonsignificant associations, need to be confirmed with future studies.

This research has strengths as well. The large size of the cohort, the long period of follow-up and the fact that it is population-based make it strong. The size aids statistical power; the follow-up allows for better interpretation of the results. Including all women makes the findings generalizable to the women of Ontario rather than a subgroup within the province. The size and range of the cohort made it possible to examine many types of procedures. Had a certain age restriction been in place, some of the procedures, which tend to be related with certain age groups, may not have been included. As well, colon and rectal cancers were examined separately and then together. As

colorectal cancer, possible misclassification was taken into consideration, while separate analyses recognized the potential differences in the cancer sites. When proximal and distal colorectal cancers were observed, diagnoses that were listed as unknown colon or rectal, were excluded, providing for much more accurate groups.

Conclusions

In summary, the nature of this investigation and study limitations make it difficult to make any firm conclusions. The findings do indicate that a more detailed exploration of this issue is necessary. The procedures may not have changed the endogenous hormone output. It is also possible that any changes to the hormone levels did not contribute to alter cancer risk. Alternatively procedures may have had an effect that was superceded by other variables (e.g. other hormone exposure). Whatever did cause the changes in risk could not be determined due to the limiting nature of the data source.

The reduced cancer risks found may be attributed to having had a procedure, however it is more likely that women who have these procedures are protected by some other factors, such as unmeasured potential confounders. This is supported by the fact that the various cancer sites examined produced similar results. Specifically, stomach cancer risk is reduced as well as that of the large intestine, for the most part. The literature seems to show that one would expect opposite types of results. Expectations were based on the literature which perhaps should be expanded. For example: ovarian disruption could be studied with better accuracy regarding many types of sterilization procedures and the amount of time required for ovarian function to diminish; the causal pathway through hormone replacement therapy needs to be elucidated. As well, the amount of

ovarian dysfunction could be quantified, including a range of percentage of women expected to have dysfunction following certain gynecological surgical procedures. The effects of endogenous estrogen exposure needs to be expanded examining lifetime exposure, controlling for parity and hormone replacement therapy, as well as other variables that could alter circulating estrogen levels.

Given the present state of knowledge in this area (both laboratory and epidemiologic), the number of women who have gynecological surgery, and the impact of stomach, colon and rectal cancer, further work is warranted. It may be worthwhile to separately examine the effects of endogenous estrogen on cancer by taking into consideration lifetime exposure while controlling for other factors. As well, ovarian changes should be examined in relation to the different kinds of specific procedures and with long follow-up periods. Moreover, specific study should be on the women who have these procedures since at present hysterectomy is focused upon rather than tubal sterilization or ovariectomy. Ultimately, the information gained from further investigations, in addition to helping elucidate the role of endogenous hormones in the development of digestive cancer, may also help to advance knowledge in other research areas related to the health of women.

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APPENDIX I

Canadian Classification of Surgical Procedures (Statistics Canada Health Division, 1986)

XIII. OPERATIONS ON THE FEMALE GENITAL ORGANS

77 OPERATIONS ON OVARY

77.0 Oophorotomy

Drainage (abscess) (cyst)
Oophorostomy
Oophorotomy
Rupture of cyst
Salpingo-oophorotomy

77.1 Local excision or destruction of lesion or tissue of ovary

77.11 Marsupialization of ovarian cyst

77.12 Wedge resection of ovary

77.19 Other local excision or destructon of ovary

Bisection
Capsulectomy
Cauterization
Coagulation
Decortication
Electrocoagulation
Enucleation of cyst
Excision of cyst
Excisional biopsy of ovary
Oophorocystectomy
Ovarian cystectomy
Partial excision of ovary
Partial oophorectomy

77.2 Unilateral oophorectomy

Oophorectomy, unqualified
Unilateral excision of ovary

77.3 Unilateral salpingo-oophorectomy

Salpingo-oophorectomy, unqualified
Unilateral excision of ovary with tube

77.4 Bilateral oophorectomy

77.41 Removal of both ovaries (at same operative episode)

Bilateral excision of ovary
Female castration

77.42 Removal of remaining ovary

Removal of solitary ovary

77.5 Bilateral salpingo-oophorectomy

Bilateral excision of ovary with tube

77.51 Removal of both ovaries and tubes (at same operative episode)

77.52 Removal of remaining ovary and tube

Removal of solitary ovary and tube

77.6 Repair of ovary

Excludes: salpingo-oophorostomy (78.62)

77.61 Suture of ovary

Oophororrhaphy
Simple suture

77.62 Reimplantation of ovary

Autotransplant of ovary
Estes operation
Implantation of ovary into uterine cavity

Excludes: homotransplant of ovary (77.92)

77.63 Salpingo-oophoroplasty

77.69 Other repair of ovary

Oophoropexy
Oophoroplasty
Salpingo-oophororrhaphy
Suspension of ovary

77.7 Freeing of adhesions of ovary and fallopian tube

Lysis of tubo-ovarian adhesions

77.8 **Invasive diagnostic procedures on ovary**

77.81 Aspiration biopsy of ovary

77.82 Other biopsy of ovary

Excludes: excisional biopsy (77.19)

77.89 Other invasive diagnostic procedures on ovary

77.9 **Other operations on ovary**

77.91 **Aspiration of ovary**

Excludes: aspiration biopsy (77.81)

77.92 **Transplantation of ovary**

Homotransplant of ovary

Excludes: reimplantation of ovary (77.62)

77.93 **Manual rupture of ovarian cyst**

77.94 **Ovarian denervation**

77.95 **Release of torsion of ovary**

77.99 Other operations on ovary NEC

78 OPERATIONS ON FALLOPIAN TUBES

78.0 **Salpingotomy**

Drainage
Incision
Removal of foreign body } of fallopian tubes

78.1 **Total salpingectomy (unilateral)**

Salpingectomy, unqualified

78.2 **Total bilateral salpingectomy**

Excludes *bilateral partial salpingectomy (for sterilization) (78.53)*
bilateral salpingo-oophorectomy (77.51)

78.21 **Removal of both tubes (at same operative episode)**

78.22 **Removal of remaining tube**

Removal of solitary tube

78.3 **Bilateral endoscopic destruction or occlusion of fallopian tubes**

That by:
cauterization
culdoscopy
endoscopy
hysteroscopy
laparoscopy
peritoneoscopy
That of remaining or solitary tube

78.31 **Bilateral endoscopic ligation and crushing of fallopian tubes**

78.32 **Bilateral endoscopic ligation and division of fallopian tubes**

78.39 **Other bilateral endoscopic destruction or occlusion of fallopian tubes**

78.4 **Other bilateral destruction or occlusion of fallopian tubes**

That of remaining or solitary tube

Excludes: *that by endoscopy (78.31-78.39)*

78.41 Other bilateral ligation and crushing of fallopian tubes

Madlener operation

78.42 Other bilateral ligation and division of fallopian tubes

Irving operation
Pomeroy operation

78.49 Other bilateral destruction or occlusion of fallopian tubes NEC

78.5 Other salpingectomy

Cauterization
Coagulation
Electrocoagulation

Excludes: fistulectomy (78.63)

78.51 Excision or destruction of lesion of fallopian tube

Excision of hydatid of Morgagni
Excisional biopsy of fallopian tube

78.52 Salpingectomy (partial) with removal of tubal pregnancy

Removal of ectopic fetus from fallopian tube

Code also associated oophorectomy (77.2)

78.53 Bilateral partial salpingectomy, unqualified

That for sterilization

78.59 Other partial salpingectomy

Cornual resection
Fimbriectomy
Kroener operation

78.6 Repair of fallopian tube

Repair of fallopian tube with graft or prosthesis

78.61 Suture of fallopian tube

Salpingorrhaphy
Simple suture

78.62 Salpingo-oophorostomy

78.63 Salpingo-salpingostomy

Repair of fistula NOS
Tubal anastomosis NOS

78.64 Salpingo-uterostomy

Hysterosalpingostomy
Implantation of tube into uterus
Reimplantation of tube into uterus
Salpingohysterostomy

78.69 Other repair of fallopian tube

Graft of fallopian tube
Removal of ligature from fallopian tube
Reopening of divided tube
Salpingoplasty
Salpingostomy

78.7 Insufflation of fallopian tube

Insufflation of fallopian tube with:
air
dye
gas
saline
Rubin's test

Excludes: insufflation of therapeutic agent (78.95)
that for hysterosalpingography (80.84, 80.85)

78.8 Invasive diagnostic procedures on fallopian tubes

Excludes: Rubin's test (78.7)

78.81 Biopsy of fallopian tube

Excludes: excisional biopsy (78.51)

78.89 Other invasive diagnostic procedures on fallopian tubes

78.9 Other operations on fallopian tubes

78.91 Aspiration of fallopian tube

78.92 Unilateral destruction or occlusion of fallopian tube

Unilateral:
division
ligation
transection
} of fallopian tube

Excludes: that of remaining tube (78.31-78.39,78.41-78.49)

78.93 Implantation or replacement of tubal prosthesis

Mulligan (Rock) hood
Silastic tube
Stent

Excludes: that with simultaneous repair of fallopian tube (78.61-78.69)

78.94 Removal of tubal prosthesis

Mulligan (Rock) hood
Silastic tube

78.95 Insufflation of therapeutic agent into fallopian tubes

78.96 Tubal dilation

78.97 Burying of fimbriae in uterine wall

Aldrich operation

78.99 Other operations on fallopian tubes NEC

Excludes: freeing of adhesions of ovary and tube (77.7)

79.8 Invasive diagnostic procedures on cervix

Excludes conization biopsy (79.1)
excisional biopsy (79.29)

79.81 Endocervical biopsy

79.82 Other cervical biopsy

Punch biopsy NOS

79.89 Other invasive and diagnostic procedures on cervix

79.9 Other operations on cervix NEC

80 OTHER INCISION AND EXCISION OF UTERUS

80.0 Hysterotomy

Hysterotomy with removal of hydatidiform mole
(Hystero) trachelotomy
That for:
drainage
exploration
removal of foreign body

Excludes: hysterotomy for termination of pregnancy (86.41)
that for excision or destruction of lesion of uterus (80.11-80.19)

80.1 Excision or destruction of lesion or tissue of uterus

80.11 Division of endometrial synechiae

Freeing of intraluminal adhesions

80.12 Incision or excision of congenital septum of uterus

80.19 Other excision or destruction of lesion of uterus

Endometrectomy
Excisional biopsy of lesion of uterus
Myomectomy

Excludes fistulectomy (81.52)

80.2 Subtotal abdominal hysterectomy

Bell Beuttner operation
Bisection, Supracervical, Supravaginal } hysterectomy
Uterine fundectomy

Excludes: hysterotrachelectomy (79.3)

80.3 Total abdominal hysterectomy

Hysterectomy, unqualified
Panhysterectomy

Code also simultaneous removal of tubes and ovaries (77.51)

80.4 Vaginal hysterectomy (subtotal) (total)

Colpohysterectomy

Code also: simultaneous removal of tubes and ovaries (77.51)
simultaneous repair of cystocele or rectocele (82.4)
simultaneous repair of pelvic floor (82.69)

80.5 Radical abdominal hysterectomy

Hysterocolpectomy
Radical hysterectomy (modified)
Removal of upper vagina and cellular tissues
Wertheim's operation

Code also: simultaneous lymph gland dissection (52.2, 52.4)
simultaneous removal of tubes and ovaries (77.51)

80.6 Radical vaginal hysterectomy

Schauta operation

Code also: simultaneous lymph gland dissection (52.2, 52.4)
simultaneous removal of tubes and ovaries (77.51)

80.7 *Pelvic evisceration*

En masse resection of all pelvic viscera
Pelvic exenteration
Removal of ovaries, tubes, uterus, vagina, bladder and urethra
That with removal of sigmoid colon and rectum

Code also: ***simultaneous colostomy (58.11-58.13)***
simultaneous lymph gland dissection (52.2, 52.4)
simultaneous urinary diversion (68.41-68.63)

80.8 Invasive diagnostic procedures on uterus and supports

Excludes: ***diagnostic aspiration curettage (81.69)***
diagnostic D & C (81.09)

80.81 Hysteroscopy

80.82 Digital examination of uterus

80.83 Uterine biopsy

Excludes: ***excisional biopsy (81.19)***

80.84 Gas contrast hysterosalpingography

80.85 Opaque dye contrast hysterosalpingography

80.86 Percutaneous hysterography

80.87 Pelvic gas contrast radiography

Pelvic pneumoperitoneum

80.88 Pelvic opaque dye contrast radiography

80.89 Other invasive diagnostic procedures on uterus and supports NEC

Biopsy of uterine ligaments

APPENDIX II

AGE-STRATIFIED ANALYSIS

Table A2.1 Stomach Cancer Age-Stratified Relative Risk Estimates and 95% Confidence Intervals (CI)- **'Ever' and Only'** Had a Procedure

Unilateral Oophorectomy

ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	31562	262064.3	1	4.6	0.22(0.00-1.10)
37-49	30582	234992.1	9	14.2	0.63(0.29-1.20)
50-64	5607	40809.6	7	6.0	0.81(0.30-1.75)
Total	67751	53766.0			

Breslow-Day chi-squared statistic (interaction)=1.7 (p>0.05) Breslow-Day chi-squared statistic (trend)=1.5 (p>0.05)

only insufficient data

Bilateral Tubal Sterilization

ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	218091	1678701.8	16	27.9	0.57(0.33-0.93)
37-49	55301	397100.8	12	19.8	0.61(0.31-1.06)
50-64	763	5664.7	1	0.9	1.10(0.01-5.55)
Total	274155	2081467.0			

Breslow-Day chi-squared statistic (interaction)=0.4 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.2 (p>0.05)

only insufficient data

Hysterectomy

ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	65535	537078.7	7	11.0	0.63(0.25-1.30)
37-49	99926	745896.3	18	45.0	0.40(0.24-0.63)
50-64	22585	172546.3	23	33.5	0.69(0.44-1.03)
Total	188046	1455521.0			

Breslow-Day chi-squared statistic (interaction)=3.2 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.8 (p>0.05)

only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	39143	328020.1	4	7.0	0.57(0.15-1.44)
37-49	66019	497182.7	12	30.2	0.40(0.21-0.69)
50-64	17733	137755.4	19	27.5	0.69(0.42-1.08)
Total	122895	962958.3			

Breslow-Day chi-squared statistic (interaction)=2.3 (p>0.05) Breslow-Day chi-squared statistic (trend)=1.0 (p>0.05)

Table A2.2 Colon Cancer Age-Stratified Relative Risk Estimates and 95% Confidence Intervals (CI)- 'Ever' and 'Only' Had a Procedure

Unilateral Oophorectomy
ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	31550	262001.0	11	15.1	0.73(0.36-1.30)
37-49	30510	234468.1	52	58.3	0.89(0.67-1.17)
50-64	5425	39989.5	39	34.9	1.12(0.80-1.53)
Total	67485	536458.5			

Breslow-Day chi-squared statistic (interaction)=2.0 (p>0.05) Breslow-Day chi-squared statistic (trend)=2.0 (p>0.05)

only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	13212	104689.1	3	4.7	0.63(0.10-1.82)
37-49	6549	47034.8	5	11.3	0.44(0.14-1.02)
50-64	2517	17296.5	21	16.2	1.30(0.80-1.98)
Total	22278	169020.5			

Breslow-Day chi-squared statistic (interaction)=5.8 (p>0.05) Breslow-Day chi-squared statistic (trend)=3.9 (p<0.05)

Unilateral Tubal Sterilization

ever					
Age (years)	No. In Group	Person-years	Observed Events	Expected Events	**RR(95% CI)**
15-36	22760	168149.8	7	7.2	**0.97(0.39-1.99)**
37-49	4991	34730.7	5	7.2	**0.69(0.22-1.60)**
50-64	507	3750.3	1	3.3	**0.30(0.00-1.54)**
Total	28258	206630.7			

Breslow-Day chi-squared statistic (interaction)=1.4 (p>0.05) Breslow-Day chi-squared statistic (trend)=1.4 (p>0.05)

only insufficient data

Bilateral Tubal Sterilization

ever					
Age (years)	No. In Group	Person-years	Observed Events	Expected Events	**RR(95% CI)**
15-36	218081	1678415.8	69	91.5	**0.75(0.59-0.95)**
37-49	55286	396803.6	58	77.1	**0.75(0.57-0.97)**
50-64	760	5641.9	5	4.4	**1.13(0.36-2.61)**
Total	274127	2080861.0			

Breslow-Day chi-squared statistic (interaction)=0.8 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.2 (p>0.05)

only					
Age (years)	No. In Group	Person-years	Observed Events	Expected Events	**RR(95% CI)**
15-36	191933	1423989.1	59	77.1	**0.77(0.58-0.99)**
37-49	47142	326275.9	45	62.0	**0.73(0.530-.97)**
50-64	293	2382.3	3	1.8	**1.71(0.34-4.92)**
Total	239368	1752647.0			

Breslow-Day chi-squared statistic (interaction)=2.2 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.1 (p>0.05)

Hysterectomy ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	65522	536949.8	27	37.6	0.72(0.47-1.04)
37-49	99884	7845229.7	152	185.2	0 .82(0.70-0.96)
50-64	22517	171823.1	160	159.1	1.01(0.86-1.17)
Total	187923	1454003.0			

Breslow-Day chi-squared statistic (interaction)=4.7 (p>0.05) Breslow-Day chi-squared statistic(trend)=4.5 (p<0.05)

only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	39140	327971.9	19	24.0	0.79(0.48-1.23)
37-49	66005	496856.8	85	124.3	0.68(0.55-0.85)
50-64	17704	137284.4	132	130.3	1.01(0.85-1.20)
Total	122849	962113.0			

Breslow-Day chi-squared statistic (interaction)=8.4 (p<0.03) Breslow-Day chi-squared statistic (trend)=5.5 (p<0.03)

Hysterectomy plus Bilateral Salpingo-oophorectomy ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	8686	68549.0	1	5.0	0.20(0.00-1.02)
37-49	39779	291974.6	87	93.4	0.93(0.75-1.15)
50-64	29324	210968.5	155	179.9	0.86(0.73-1.01)
Total	77789	571492.1			

Breslow-Day chi-squared statistic (interaction)=3.0 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.02 (p>0.05)

only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	7362	59823.7	1	4.5	0.22(0.00-1.13)
37-49	37582	280610.2	83	90.8	0.91(0.73-1.13)
50-64	28989	209433.9	147	178.9	0.82(0.69-0.97)
Total	73933	549867.8			

Breslow-Day chi-squared statistic (interaction)=2.7 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.02 (p>0.05)

Table A2.3 Rectal Cancer Age-Stratified Relative Risk Estimates and 95% Confidence Intervals (CI)- 'Ever' and 'Only' Had a Procedure

Unilateral Oophorectomy

ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	31555	262030.9	6	5.5	1.10(0.40-2.37)
37-49	30561	234810.4	18	25.9	0.69(0.41-1.10)
50-64	5528	40414.9	25	13.7	1.83(1.18-2.70)
Total	67644	537256.3			

Breslow-Day chi-squared statistic (interaction)=10.6 ($p<0.01$) Breslow-Day chi-squared statistic (trend)=5.3($p<0.03$)

only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	13216	104700.8	3	1.8	1.68(0.34-4.81)
37-49	6589	47213.7	7	5.0	1.41(0.56-2.89)
50-64	2609	17693.6	12	6.4	1.88(0.97-3.28)
Total	22414	169608.1			

Breslow-Day chi-squared statistic (interaction)=0.4 ($p>0.05$) Breslow-Day chi-squared statistic (trend)=0.2 ($p>0.05$)

Bilateral Tubal Sterilization

ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	218086	167859.3	37	33.7	1.10(0.77-1.51)
37-49	55297	397010.3	25	33.8	0.74(0.48-1.09)
50-64	755	5624.0	3	1.7	1.73(0.35-4.97)
Total	274138	2081225.0			

Breslow-Day chi-squared statistic (interaction)=3.5 ($p>0.05$) Breslow-Day chi-squared statistic (trend)=0.8 ($p>0.05$)

only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	191933	1424126.0	30	28.3	1.06(0.71-1.51)
37-49	47144	326265.3	19	27.0	0.70(0.42-1.10)
50-64	291	2382.3	2	0.7	2.90(0.33-10.10)
Total	239368	1752874.0			

Breslow-Day chi-squared statistic (interaction)=5.0 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.6 (p>0.05)

Hysterectomy

ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	65523	536981.6	18	13.2	1.37(0.81-2.16)
37-49	99917	745753.5	64	81.4	0.79(0.61-1.00)
50-64	22536	172183.5	58	61.5	0.94(0.72-1.22)
Total	187976	1454919.0			

Breslow-Day chi-squared statistic (interaction)=8.0 (p<0.03) Breslow-Day chi-squared statistic (trend)=6.4 (p<0.03)

only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	39138	327966.4	10	8.41	1.19(0.57-2.18)
37-49	66017	497105.9	39	54.70	0.71(0.51-0.98)
50-64	17708	137515.5	40	50.23	0.80(0.57-1.08)
Total	122863	962587.9			

Breslow-Day chi-squared statistic (interaction)=2.1 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.2 (p>0.05)

Hysterectomy plus Bilateral Salpingo-oophorectomy

ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	8694	68579.0	3	1.74	1.72(0.35-4.95)
37-49	39831	292309.3	30	41.29	0.73(0.49-1.04)
50-64	29391	211565.6	52	70.06	0.74(0.55-0.97)
Total	77916	572453.9			

Breslow-Day chi-squared statistic (interaction)=2.2 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.2 (p>0.05)

only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	7371	59872.9	3	1.56	1.92(0.39-5.52)
37-49	37626	280892.8	29	40.24	0.72(0.48-1.04)
50-64	29056	210026.2	51	69.66	0.73(0.55-0.96)
Total	74053	550791.9			

Breslow-Day chi-squared statistic (interaction)=3.0 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.3 (p>0.05)

Table A2.4 Colorectal Cancer Age-Stratified Relative Risk Estimates and 95% Confidence Intervals (CI)- 'Ever' and 'Only' Had a Procedure

Unilateral Oophorectomy

ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	31542	261947.8	17	20.61	0.82(0.48-1.32)
37-49	30481	234255.2	70	84.22	0.83(0.65-1.05)
50-64	5343	39553.9	64	47.83	1.34(1.03-1.71)
Total	67366	535756.6			

Breslow-Day chi-squared statistic (interaction)=8.6 (p<0.03) Breslow-Day chi-squared statistic (trend)=6.4 (p<0.03)

only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	13103	104374.3	7	6.55	1.07(0.43-2.19)
37-49	6575	46928.2	12	16.30	0.74(0.38-1.28)
50-64	2524	17204.3	33	22.45	1.47(1.01-2.06)
Total	22142	168506.8			

Breslow-Day chi-squared statistic (interaction)=4.5 (p>0.05) Breslow-Day chi-squared statistic (trend)=2.2 (p>0.05)

Unilateral Tubal Sterilization

ever					
Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	22760	168149.8	9	9.98	0.90(0.41-1.71)
37-49	4988	34696.1	10	10.32	1.00(0.48-1.84)
50-64	504	3732.6	2	4.55	0.44(0.05-1.53)
Total	28252	206578.5			

Breslow-Day chi-squared statistic (interaction)=1.1 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.5 (p>0.05)

only insufficient data

Bilateral Tubal Sterilization

ever					
Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	218075	1678280.1	106	125.7	0.84(0.69-1.02)
37-49	55279	396671.1	83	111.1	0.75(0.60-0.93)
50-64	752	5600.7	8	6.1	1.30(0.56-2.56)
Total	274106	2080552.0			

Breslow-Day chi-squared statistic (interaction)=2.6 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.01 (p>0.05)

only					
Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	191323	1423913.5	89	105.9	0.84(0.68-1.03)
37-49	47138	326176.8	64	89.1	0.72(0.55-0.92)
50-64	290	2372.9	5	2.4	2.07(0.67-4.78)
Total	239360	1752463.0			

Breslow-Day chi-squared statistic (interaction)=5.8 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.03 (p>0.05)

Hysterectomy ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	65510	536836.3	45	51.0	0.88(0.64-1.18)
37-49	99862	745000.8	216	256.8	0.84(0.73-0.96)
50-64	22466	171418.2	218	220.2	0.99(0.86-1.13)
Total	187838	1453255.0			

Breslow-Day chi-squared statistic (interaction)=2.9 (p>0.05) Breslow-Day chi-squared statistic (trend)=1.9 (p>0.05)

only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	39135	327903.0	29	32.6	0.89(0.60-1.28)
37-49	65997	496744.6	124	179.2	0.69(0.58-0.83)
50-64	17678	137023.4	172	180.3	0.95(0.82-1.11)
Total	122810	961671.1			

Breslow-Day chi-squared statistic (interaction)=7.6 (p<0.03) Breslow-Day chi-squared statistic (trend)=3.3 (p>0.05)

Hysterectomy plus Bilateral Salpingo-oophorectomy ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	8681	68511.4	4	6.7	0.59(0.16-1.50)
37-49	39746	291740.0	117	134.6	0.87(0.72-1.04)
50-64	29249	210539.4	207	249.4	0.83(0.72-0.95)
Total	77676	570790.8			

Breslow-Day chi-squared statistic (interaction)=0.7 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.01 (p>0.05)

only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	7360	59810.8	4	6.1	0.66(0.18-1.67)
37-49	37552	280378.7	112	131.0	0.86(0.70-1.03)
50-64	28916	209007.6	198	248.0	0.80(0.69-0.92)
Total	73828	549197.0			

Breslow-Day chi-squared statistic (interaction)=0.5 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.1 (p>0.05)

Table A2.5 Proximal Colorectal Cancer Age-Stratified Relative Risk Estimates and 95% Confidence Intervals (CI)- 'Ever' and 'Only' Had a Procedure

Unilateral Oophorectomy

ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	31559	262040.4	3	5.2	0.57(0.12-1.65)
37-49	30566	234857.0	16	19.9	0.81(0.46-1.31)
50-64	5561	40626.2	9	14.2	0.64(0.29-1.20)
Total	67686	537523.6			

Breslow-Day chi-squared statistic (interaction)=0.5 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.01 (p>0.05)

only insufficient data

Bilateral Tubal Sterilization

ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	218084	1678608.2	21	32.2	0.65(0.40-1.00)
37-49	55299	397045.1	18	25.8	0.70(0.41-1.10)
50-64	763	5655.3	2	1.7	1.15(0.13-4.01)
Total	274146	2081308.0			

Breslow-Day chi-squared statistic (interaction)=0.6 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.3 (p>0.05)

only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	191933	1424137.8	18	27.3	0.66(0.39-1.04)
37-49	47147	326406.8	14	20.6	0.68(0.37-1.14)
50-64	294	2390.4	1	0.7	1.52(0.02-7.66)
Total	239374	1752935.0			

Breslow-Day chi-squared statistic (interaction)=0.7 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.1 (p>0.05)

Hysterectomy
ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	65527	537018.3	14	12.6	1.11(0.61-1.86)
37-49	99918	745710.0	50	62.9	0.80(0.59-1.05)
50-64	22571	172330.8	62	64.6	0.96(0.74-1.23)
Total	188016	1455059.0			

Breslow-Day chi-squared statistic (interaction)=1.6 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.03 (p>0.05)

only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	39142	328027.3	10	8.0	1.25(0.60-2.30)
37-49	66015	49709.4	29	42.2	0.69(0.46-0.99)
50-64	17730	137614.8	54	53.2	1.01(0.76-1.32)
Total	122887				

Breslow-Day chi-squared statistic (interaction)=4.0 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.3 (p>0.05)

Hysterectomy plus Bilateral Salpingo-oophorectomy
ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	8693	68584.5	2	1.7	1.19(0.13-4.15)
37-49	39826	292321.1	25	32.5	0.77(0.50-1.14)
50-64	29411	211599.5	52	71.5	0.73(0.54-0.95)
Total	77930	572505.1			

Breslow-Day chi-squared statistic (interaction)=0.5 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.2 (p>0.05)

only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	7369	59859.2	1	1.2	0.87(0.01-4.39)
37-49	37621	280911.5	24	31.6	0.76(0.49-1.13)
50-64	29074	210060.9	51	71.1	0.72(0.53-0.94)
Total	74064	550831.5			

Breslow-Day chi-squared statistic (interaction)=0.8 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.1 (p>0.05)

Table A2.6 Distal Colorectal Cancer Age-Stratified Relative Risk Estimates and 95% Confidence Intervals (CI)- 'Ever' and 'Only' Had a Procedure

Unilateral Oophorectomy

ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	31552	262013.4	6	11.7	0.51(0.19-1.11)
37-49	30520	234538.5	34	51.1	0.66(0.46-0.93)
50-64	5439	40023.3	27	26.2	1.03(0.68-1.50)
Total	67511	536575.2			

Breslow-Day chi-squared statistic (interaction)=4.1 (p>0.05) Breslow-Day chi-squared statistic (trend)=3.8 (p>0.05)

only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	13213	104697.8	3	3.7	0.82(0.17-2.36)
37-49	6559	47062.1	7	9.9	0.71(0.28-1.45)
50-64	2533	17342.5	13	12.0	1.08(0.58-1.85)
Total	22305	169102.3			

Breslow-Day chi-squared statistic (interaction)=0.9 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.5 (p>0.05)

Bilateral Tubal Sterilization

ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	218085	1678447.2	70	71.0	0.99(0.77-1.25)
37-49	55288	396854.4	51	67.5	0.76(0.56-0.99)
50-64	752	5613.7	4	3.4	1.18(0.32-3.00)
Total	274125	2080915.0			

Breslow-Day chi-squared statistic (interaction)=2.5 (p>0.05) Breslow-Day chi-squared statistic (trend)=1.1 (p>0.05)

only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	191935	1424026.3	60	59.6	1.00(0.77-1.30)
37-49	47141	326291.6	41	54.2	0.76(0.54-1.03)
50-64	290	2377.3	2	1.4	1.47(0.17-5.13)
Total	239366	1752695.0			

Breslow-Day chi-squared statistic (interaction)=2.5 (p>0.05) Breslow-Day chi-squared statistic (trend)=1.2 (p>0.05)

Hysterectomy
ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	65522	536943.4	22	29.2	0.75(0.47-1.14)
37-49	99893	745413.4	114	161.7	0.71(0.58-0.85)
50-64	22510	171886.8	101	117.9	0.86(0.70-1.04)
Total	187925	1454244.0			

Breslow-Day chi-squared statistic (interaction)=2.1 (p>0.05) Breslow-Day chi-squared statistic (trend)=1.3 (p>0.05)

only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	39138	327937.6	13	18.7	0.69(0.37-1.10)
37-49	66012	496974.0	73	108.6	0.67(0.53-0.85)
50-64	17698	137322.3	80	96.1	0.83(0.66-1.04)
Total	122848	962233.9			

Breslow-Day chi-squared statistic (interaction)=1.8 (p>0.05) Breslow-Day chi-squared statistic (trend)=1.4 (p>0.05)

Hysterectomy plus Bilateral Salpingo-oophorectomy
ever

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	8690	68559.9	1	3.9	0.26(0.00-1.31)
37-49	39793	292097.8	50	81.0	0.62(0.46-0.81)
50-64	29328	211120.5	78	135.3	0.58(0.46-0.72)
Total	77815	571778.3			

Breslow-Day chi-squared statistic (interaction)=0.9 (p>0.05) Breslow-Day chi-squared statistic (trend)< 0.01(p>0.05)

only

Age (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
15-36	7367	59853.8	1	3.5	0.29(0.00-1.46)
37-49	37596	280707.6	49	78.8	0.62(0.46-0.82)
50-64	28996	209590.9	78	134.5	0.58(0.46-0.72)
Total	73959	550152.3			

Breslow-Day chi-squared statistic (interaction)=0.7 (p>0.05) Breslow-Day chi-squared statistic (trend)< 0.01(p>0.05)

TIME-STRATIFIED ANALYSIS

Table A2.7 Stomach Cancer Time-Stratified Relative Risk Estimates and 95% Confidence Intervals (CI)- **'Ever' and 'Only'** Had a Procedure

Unilateral Oophorectomy

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	67751	131923.8	4	4.3	0.93(0.25-2.35)
2-4.9	62039	165859.3	3	6.6	0.45(0.09-1.30)
5-15	48693	240082.9	9	15.3	0.59(0.27-1.12)
Total	67751	537866.0			

Breslow-Day chi-squared statistic (interaction)=1.0 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.3 (p>0.05)

only insufficient data

Bilateral Tubal Sterilization

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	274155	526917.0	5	7.5	0.67(0.22-1.55)
2-4.9	239496	604472.2	6	10.3	0.58(0.21-1.26)
5-15	176181	950077.8	28	30.9	0.91(0.60-1.31)
Total	274155	2081467.0			

Breslow-Day chi-squared statistic (interaction)=1.2 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.8 (p>0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	239376	458199.4	5	6.3	0.79(0.26-1.83)
2-4.9	206196	511450.9	4	8.5	0.47(0.13-1.20)
5-15	147290	783390.4	15	25.1	0.60(0.33-0.99)
Total	239376	1753041.0			

Breslow-Day chi-squared statistic (interaction)=0.6 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.1 (p>0.05)

Hysterectomy
ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	188046	365932.9	6	15.0	0.40(0.15-0.89)
2-4.9	171176	453782.6	16	23.1	0.69(0.40-1.12)
5-15	131325	635805.6	26	51.5	0.50(0.33-0.74)
Total	188046	1455521.0			

Breslow-Day chi-squared statistic (interaction)=1.7 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.01 (p>0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	122895	239387.6	5	10.7	0.47(0.15-1.08)
2-4.9	112172	297610.7	10	16.7	0.60(0.29-1.10)
5-15	86345	425960.0	20	37.3	0.54(0.33-0.83)
Total	122895	962958.3			

Breslow-Day chi-squared statistic (interaction)=0.2 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.02 (p>0.05)

Hysterectomy plus Bilateral Salpingo-oophorectomy
ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	778011	150570.7	8	11.0	0.73(0.31-1.42)
2-4.9	69472	180440.9	13	16.3	0.80(0.42-1.36)
5-15	51417	242014.5	21	33.0	0.64(0.39-0.97)
Total	778011	573026.1			

Breslow-Day chi-squared statistic (interaction)=0.4 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.2 (p>0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	74140	143294.1	8	10.8	0.74(0.32-1.46)
2-4.9	66302	172644.2	13	16.0	0.81(0.43-1.39)
5-15	49437	235251.7	21	32.6	0.64(0.40-0.98)
Total	74140	551333.8			

Breslow-Day chi-squared statistic (interaction)=0.5 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.3 (p>0.05)

Table A2.8 Colon Cancer Time-Stratified Relative Risk Estimates and 95% Confidence Intervals (CI)- **'Ever' and 'Only'** Had a Procedure

Unilateral Oophorectomy

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	67485	131462.3	28	16.7	**1.67(1.11-2.42)**
2-4.9	61857	165442.9	20	27.2	**0.73(0.45-1.13)**
5-15	48587	239553.2	54	64.3	**0.84(0.63-1.10)**
Total	67485	536458.5			

Breslow-Day chi-squared statistic (interaction)=11.5($p<0.01$) Breslow-Day chi-squared statistic (trend)=6.3 ($p<0.03$)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	22278	43101.0	13	5.7	**2.29(1.22-3.90)**
2-4.9	20024	52411.2	5	8.4	**0.59(0.19-1.37)**
5-15	15080	73508.2	11	18.1	**0.61(0.30-1.08)**
Total	22278	169020.5			

Breslow-Day chi-squared statistic (interaction)=14.7($p<0.01$) Breslow-Day chi-squared statistic (trend)=10.2($p<0.01$)

Unilateral Tubal Sterilization

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	28258	54785.9	7	2.7	**2.64(1.06-5.42)**
2-4.9	25469	66243.1	1	4.4	**0.23(0.00-1.14)**
5-15	18784	85601.7	5	10.7	**0.47(0.15-1.09)**
Total	28258	206630.7			

Breslow-Day chi-squared statistic (interaction)=15.8 ($p<0.01$) Breslow-Day chi-squared statistic (trend)=8.7($p<0.01$)

only insufficient data

Bilateral Tubal Sterilization

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	274127	526866.9	16	21.7	0.74(0.42-1.20)
2-4.9	239464	604356.0	36	35.3	1.02(0.72-1.41)
5-15	176135	949638.4	80	116.1	0.69(0.55-0.86)
Total	274127	2080861.0			

Breslow-Day chi-squared statistic(interaction)=7.21 (p<0.05) Breslow-Day chi-squared statistic(trend)=7.15 (p<0.01)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	239368	458184.7	13	18.2	0.71(0.38-1.22)
2-4.9	206183	511391.5	31	28.8	1.08(0.73-1.53)
5-15	147262	783071.1	63	93.8	0.67(0.52-0.86)
Total	239368	1752647.0			

Breslow-Day chi-squared statistic(interaction)=4.84 (p>0.05) Breslow-Day chi-squared statistic(trend)=1.01 (p>0.05)

Hysterectomy

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	187923	365691.2	44	61.8	0.71(0.52-0.96)
2-4.9	171066	453432.4	102	98.6	1.03(0.84-1.26)
5-15	131205	634879.2	191	221.4	0.86(0.75-0.99)
Total	187923	1454003.0			

Breslow-Day chi-squared statistic (interaction)=4.7 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.2 (p>0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	122849	239289.4	31	45.3	0.68(0.47-0.97)
2-4.9	122129	297436.9	73	72.1	1.01(0.79-1.27)
5-15	86279	425386.8	132	161.3	0.82(0.69-0.97)
Total	122849	962113.0			

Breslow-Day chi-squared statistic (interaction)=3.9 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.1 (p>0.05)

Hysterectomy plus Bilateral Salpingo-oophorectomy

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	77789	150172.6	42	51.3	0.82(0.59-1.11)
2-4.9	69320	180029.6	68	76.2	0.89(0.69-1.13)
5-15	51298	241289.8	133	150.7	0.88(0.74-1.05)
Total	77789	571492.1			

Breslow-Day chi-squared statistic (interaction)=0.2 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.1 (p>0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	73933	142921.3	40	50.2	0.80(0.57-1.08)
2-4.9	66161	172400.6	65	74.9	0.87(0.67-1.11)
5-15	49324	234545.9	126	149.0	0.85(0.70-1.01)
Total	73933	549867.8			

Breslow-Day chi-squared statistic (interaction)=0.2 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.1 (p>0.05)

Table A2.9 Rectal Cancer Time-Stratified Relative Risk Estimates and 95% Confidence Intervals (CI)- 'Ever' and 'Only' Had a Procedure

Unilateral Oophorectomy

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	67644	131730.3	12	7.8	1.54(0.79-2.68)
2-4.9	61961	165692.7	15	12.3	1.22(0.68-2.02)
5-15	48648	239833.3	22	25.0	0.88(0.55-1.33)
Total	67644	537256.3			

Breslow-Day chi-squared statistic (interaction)=2.6 (p>0.05) Breslow-Day chi-squared statistic (trend)=2.6 (p>0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	22414	43326.5	5	2.6	1.96(0.63-4.54)
2-4.9	20111	52624.6	6	3.7	1.64(0.60-3.55)
5-15	15129	73657.0	11	6.9	1.59(0.79-2.84)
Total	22414	169608.1			

Breslow-Day chi-squared statistic (interaction)=0.2 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.1 (p>0.05)

Bilateral Tubal Sterilization

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	274138	526885.5	5	10.4	0.48(0.16-1.11)
2-4.9	239482	604424.9	15	16.5	0.91(0.51-1.50)
5-15	176166	949914.2	45	42.4	1.06(0.77-1.42)
Total	274138	2081225.0			

Breslow-Day chi-squared statistic (interaction)=3.0 (p>0.05) Breslow-Day chi-squared statistic (trend)=2.8 (p>0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	239368	458183.8	4	8.6	0.47(0.13-1.18)
2-4.9	206189	511422.3	11	13.4	0.82(0.41-1.47)
5-15	147281	783267.5	36	34.1	1.06(0.74-1.46)
Total	239368	1752874.0			

Breslow-Day chi-squared statistic (interaction)=2.8 (p>0.05) Breslow-Day chi-squared statistic (trend)=2.7 (p>0.05)

Hysterectomy

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	187976	365795.6	26	27.6	0.94(0.62-1.38)
2-4.9	171114	453630.5	33	42.8	0.77(0.53-1.08)
5-15	131276	635492.6	80	85.6	0.930(.74-1.16)
Total	187976	1454919.0			

Breslow-Day chi-squared statistic (interaction)=1.0 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.1 (p>0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	122863	239321.6	15	20.1	0.75(0.42-1.23)
2-4.9	112140	297516.7	22	31.0	0.71(0.45-1.07)
5-15	86310	425749.5	52	62.3	0.84(0.62-1.09)
Total	122863	962587.9			

Breslow-Day chi-squared statistic (interaction)=0.5 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.3 (p>0.05)

Hysterectomy plus Bilateral Salpingo-oophorectomy

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	77916	150394.1	11	22.6	0.49(0.24-.87)
2-4.9	69401	180288.5	25	32.2	0.78(0.50-1.15)
5-15	51373	241771.4	49	58.3	0.84(0.62-1.11)
Total	77916	572453.9			

Breslow-Day chi-squared statistic (interaction)=2.7 (p>0.05) Breslow-Day chi-squared statistic (trend)=2.4 (p>0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	74053	143129.1	11	22.1	0.50(0.25-0.89)
2-4.9	66234	172644.2	24	31.7	0.76(0.49-1.13)
5-15	49395	235018.7	48	57.7	0.83(0.61-1.10)
Total	74053	550791.9			

Breslow-Day chi-squared statistic (interaction)=2.4 (p>0.05) Breslow-Day chi-squared statistic (trend)=2.2 (p>0.05)

Table A2.10 Colorectal Cancer Time-Stratified Relative Risk Estimates and 95% Confidence Interval (CI)- 'Ever' and 'Only' Had a Procedure

Unilateral Oophorectomy

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	67366	131250.5	40	24.4	1.64(1.17-2.24)
2-4.9	61771	165248.9	34	39.3	0.86(0.60-1.21)
5-15	48534	239257.3	77	89.0	0.87(0.68-1.08)
Total	67366	535756.6			

Breslow-Day chi-squared statistic (interaction)=12.5 (p<0.01) Breslow-Day chi-squared statistic (trend)=8.5(p<0.01)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	22142	43101.0	18	8.3	2.18(1.29-3.45)
2-4.9	19849	52411.2	11	12.1	0.91(0.45-1.63)
5-15	14948	73508.2	22	25.0	0.88(0.55-1.33)
Total	22142	168506.8			

Breslow-Day chi-squared statistic (interaction)=10.0 (p<0.01) Breslow-Day chi-squared statistic (trend)=7.2(p<0.01)

Unilateral Tubal Sterilization

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	28252	54776.3	9	3.9	2.30(1.05-4.36)
2-4.9	25465	66231.1	1	6.4	0.16(0.00-0.79)
5-15	18780	85571.1	9	14.5	0.62(0.28-1.17)
Total	28252	206578.5			

Breslow-Day chi-squared statistic (interaction)=15.6 (p<0.01) Breslow-Day chi-squared statistic (trend)=6.2 (p<0.03)

only insufficient data

Bilateral Tubal Sterilization

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	274106	526824.3	21	32.2	0.65(0.40-1.00)
2-4.9	239444	604294.5	51	52.0	0.98(0.73-1.29)
5-15	176117	949433.0	121	158.8	0.76(0.63-0.91)
Total	274106	2080552.0			

Breslow-Day chi-squared statistic (interaction)=3.3 (p>0.05) Breslow-Day chi-squared statistic (trend)<0.01(p>0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	239360	458168.3	17	26.9	0.63(0.37-1.01)
2-4.9	206174	511360.6	42	42.3	0.99(0.72-1.34)
5-15	147253	782934.2	99	128.2	0.77(0.63-0.94)
Total	239360	1752463.0			

Breslow-Day chi-squared statistic (interaction)=3.0 (p>0.05) Breslow-Day chi-squared statistic (trend)=1.1(p>0.05)

Hysterectomy

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	187838	365530.5	70	89.5	0.78(0.61-0.99)
2-4.9	170993	453244.5	135	141.5	0.95(0.80-1.13)
5-15	131144	634480.3	268	306.9	0.87(0.77-0.98)
Total	187838	1453255.0			

Breslow-Day chi-squared statistic (interaction)=1.9 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.2 (p>0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	122810	239211.8	46	65.4	0.70(0.51-0.94)
2-4.9	112090	297326.6	95	103.2	0.92(0.75-1.13)
5-15	86239	425132.5	184	223.5	0.82(0.71-0.93)
Total	122810	961671.1			

Breslow-Day chi-squared statistic (interaction)=2.3 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.3 (p>0.05)

Hysterectomy plus Bilateral Salpingo-oophorectomy

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	77676	149968.0	53	73.8	0.72(0.55-0.96)
2-4.9	69238	179842.9	93	108.4	0.86(0.71-1.07)
5-15	51245	240979.9	182	208.6	0.87(0.76-1.02)
Total	77676	570790.8			

Breslow-Day chi-squared statistic (interaction)=1.6 (p>0.05) Breslow-Day chi-squared statistic (trend)=1.3 (p>0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	73828	142728.6	51	72.3	0.71(0.53-0.93)
2-4.9	66082	172222.5	89	106.5	0.84(0.67-1.03)
5-15	49273	234245.9	173	206.3	0.84(0.72-0.97)
Total	73828	549197.0			

Breslow-Day chi-squared statistic (interaction)=1.3 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.9 (p>0.05)

Table A2.11 Proximal Colorectal Cancer Relative Risk Estimates and 95% Confidence Intervals (CI)- 'Ever' and 'Only' Had a Procedure

Unilateral Oophorectomy

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	67686	131814.6	2	6.1	0.33(0.04-1.50)
2-4.9	61998	165759.5	8	9.9	0.81(0.35-1.59)
5-15	48668	239949.5	18	23.3	0.77(0.46-1.22)
Total	67686	537523.6			

Breslow-Day chi-squared statistic (interaction)=1.5 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.9 (p>0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	22440	43379.3	1	2.2	**0.46(0.00-2.33)**
2-4.9	20133	52661.2	1	3.2	**0.31(0.00-1.56)**
5-15	15142	73776.5	4	9.0	**0.45(0.12-1.13)**
Total	22440	169817.0			

Breslow-Day chi-squared statistic (interaction)=0.1 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.01 (p>0.05)

Bilateral Tubal Sterilization

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	274146	526902.5	6	8.0	**0.75(0.27-1.63)**
2-4.9	239486	604437.4	9	12.7	**0.71(0.32-1.34)**
5-15	176167	949968.4	26	39.0	**0.67(0.44-0.98)**
Total	274146	2081308.0			

Breslow-Day chi-squared statistic (interaction)=0.1 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.1 (p>0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	239374	458195.0	5	6.8	**0.74(0.24-1.71)**
2-4.9	206192	511436.3	7	10.4	**0.67(0.27-1.38)**
5-15	147282	783303.9	21	31.4	**0.67(0.41-1.02)**
Total	239374	1752935.0			

Breslow-Day chi-squared statistic (interaction)=0.04 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.03 (p>0.05)

Hysterectomy

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	188016	365874.1	14	22.3	**0.63(0.34-1.05)**
2-4.9	171151	453688.4	35	35.9	**0.97(0.68-1.36)**
5-15	131292	635496.5	77	81.9	**0.94(0.74-1.18)**
Total	188016	1455059.0			

Breslow-Day chi-squared statistic (interaction)=2.2 (p>0.05) Breslow-Day chi-squared statistic (trend)=1.3 (p>0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	122887	239372.5	10	16.5	0.61(0.29-1.11)
2-4.9	112169	297579.7	26	26.5	0.98(0.64-1.44)
5-15	86330	425784.2	57	60.5	0.94(0.71-1.22)
Total	122887	962736.4			

Breslow-Day chi-squared statistic (interaction)=1.9 (p>0.05) Breslow-Day chi-squared statistic (trend)=1.1 (p>0.05)

Hysterectomy plus Bilateral Salpingo-oophorectomy

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	77930	150420.5	17	18.8	0.90(0.53-1.44)
2-4.9	69413	180289.1	23	28.4	0.81(0.51-1.21)
5-15	51374	241795.4	39	58.4	0.67(0.48-0.91)
Total	77930	572505.1			

Breslow-Day chi-squared statistic (interaction)=1.3 (p>0.05) Breslow-Day chi-squared statistic (trend)=1.2 (p>0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	74064	143153.5	16	18.5	0.87(0.50-1.41)
2-4.9	66248	172642.3	22	27.9	0.79(0.49-1.19)
5-15	49394	235035.7	38	57.9	0.66(0.47-0.90)
Total	74064	550831.5			

Breslow-Day chi-squared statistic (interaction)=1.0 (p>0.05) Breslow-Day chi-squared statistic (trend)=1.0 (p>0.05)

Table A2.12 Distal Colorectal Cancer Time-Stratified Relative Risk Estimates and 95% Confidence Intervals (CI)- 'Ever' and 'Only' Had a Procedure

Unilateral Oophorectomy

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	67511	131498.9	14	14.6	0.96(0.52-1.61)
2-4.9	61867	165485.7	16	23.5	0.68(0.39-1.11)
5-15	48597	239590.6	37	50.9	0.73(0.51-1.00)
Total	67511	536575.2			

Breslow-Day chi-squared statistic (interaction)=1.0 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.5 (p>0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	22305	43143.8	5	4.8	1.05(0.34-2.44)
2-4.9	20040	52460.7	7	7.0	1.01(0.40-2.07)
5-15	15089	73497.8	11	13.8	0.80(0.40-1.42)
Total	22305	169102.3			

Breslow-Day chi-squared statistic (interaction)=0.4 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.4 (p>0.05)

Unilateral Tubal Sterilization

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	28265	54801.1	2	2.2	0.89(0.10-3.11)
2-4.9	25476	66260.7	1	3.7	0.27(0.00-1.36)
5-15	18789	85610.5	7	8.3	0.84(0.34-1.73)
Total	28265	20672.3			

Breslow-Day chi-squared statistic (interaction)=1.3 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.1 (p>0.05)

only insufficient data

Bilateral Tubal Sterilization

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	274125	526863.3	10	18.0	0.56(0.27-1.02)
2-4.9	239469	604377.4	32	30.5	1.05(0.72-1.48)
5-15	176147	949674.5	83	93.4	0.89(0.71-1.10)
Total	274125	2080915.0			

Breslow-Day chi-squared statistic (interaction)=3.1 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.7 (p>0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	239366	458183.1	8	15.0	0.54(0.23-1.05)
2-4.9	206187	511404.3	27	24.8	1.09(0.72-1.59)
5-15	147272	783107.8	68	75.4	0.90(0.70-1.14)
Total	239366	1752695.0			

Breslow-Day chi-squared statistic (interaction)=3.2 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.7 (p>0.05)

Hysterectomy

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	187925	365694.6	38	52.8	0.72(0.51-0.99)
2-4.9	171066	453482.8	62	83.2	0.75(0.57-0.96)
5-15	131224	635066.0	137	172.7	0.79(0.67-0.94)
Total	187925	1454244.0			

Breslow-Day chi-squared statistic(interaction)=0.4 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.4 (p>0.05)

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	122848	239289.4	25	38.4	0.65(0.42-0.96)
2-4.9	112125	297450.4	47	60.2	0.78(0.57-1.04)
5-15	86284	425494.1	94	124.8	0.75(0.61-0.92)
Total	122848	962233.9			

Breslow-Day chi-squared statistic (interaction)=0.6 (p>0.05) Breslow-Day chi-squared statistic (trend)=0.2 (p>0.05)

Hysterectomy plus Bilateral Salpingo-oophorectomy

ever

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	77815	150220.4	16	43.5	**0.37(0.21-0.60)**
2-4.9	69337	180116.5	37	62.5	**0.59(0.42-0.82)**
5-15	51322	241441.4	76	114.1	**0.67(0.53-0.83)**
Total	77815	571778.3			

Breslow-Day chi-squared statistic (interaction)=4.7 (p>0.05) **Breslow-Day chi-squared statistic (trend)=4.4 (p<0.05)**

only

Time (years)	No. In Group	Person-years	Observed Events	Expected Events	RR(95% CI)
0.5-1.9	73959	142966.1	16	42.6	**0.38(0.22-0.61)**
2-4.9	66175	172486.7	36	61.4	**0.59(0.41-0.81)**
5-15	49348	234699.5	76	112.8	**0.67(0.53-084)**
Total	73959	550152.3			

Breslow-Day chi-squared statistic (interaction)=4.7 (p>0.05) **Breslow-Day chi-squared statistic (trend)=4.4 (p<0.05)**