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Original Paper

The Risk of Breast Cancer Following Reproductive Surgery

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Alteration of exposure to ovarian hormones, by eliminating or impairing the function of one or both ovaries, may affect the risk of breast cancer. To assess the relationship between reproductive surgical procedures and breast cancer risk, we conducted a retrospective cohort study involving 524 709 Ontario women who underwent tubal ligation or other salpingectomy, hysterectomy and/or ovariectomy between 1979 and 1993. Data on type and year of surgery were obtained from hospital records and linked with breast cancer diagnoses recorded in the Ontario Cancer Registry. Observed breast cancers were compared with age- and calendar-period expected rates in Ontario. A decreased risk of breast cancer was observed among women who had undergone either hysterectomy (observed/expected [O/E] = 0.87, $P < 0.001$) or unilateral ovariectomy (O/E = 0.74, $P < 0.001$). Bilateral ovariectomy and tubal ligation were associated with reduced risk when the surgery occurred before the age of 45 years, and tubal ligation was protective if performed after the age of 54 years. There was no trend in risk with increasing follow-up. Our data support the hypothesis that reduced levels of endogenous oestrogen may be protective for breast cancer in women. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

BREAST CANCER is the most common cancer among women in North America and Europe. Both experimental and epidemiological evidence indicates that ovarian hormones are involved in the aetiology of breast cancer, thereby suggesting that ovarian function is an important determinant of breast cancer risk. Factors that affect exposure to circulating ovarian hormones (e.g. age at menarche, age at menopause) have repeatedly been associated with breast cancer risk. However, there is still much to be understood about the association between commonly performed reproductive operations, which may affect ovarian function and breast cancer risk. Results from studies that examined the association between hysterectomy and breast cancer are controversial, with the preponderance of the evidence suggesting that hysterectomy alone is not associated with breast cancer risk [1–5]. Studies examining the association between tubal ligation and breast cancer are sparse and the results contradictory [1, 3]. Several studies found bilateral ovariectomy in premenopausal women was associated with a reduced risk of subsequent breast cancer [1–6]. Unilateral ovariectomy was not found to be protective, and has even been associated with increased risk [2, 4, 5]. Therefore, to investigate further the effects of reproductive surgeries on breast cancer risk, data from a population-based historical cohort were used in this study.

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MATERIALS AND METHODS

Full details of the cohort have been published elsewhere [7]. Briefly, records of the Hospital Medical Records Institute (HMRI) of all women in Ontario having undergone reproductive surgery between April 1979 and March 1993, were obtained from the Ontario Ministry of Health (MOH). We included women who had a tubal ligation or other salpingectomy, hysterectomy and/or ovariectomy, based on the codes in the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures [8]. Three probabilistic record linkages were conducted: an internal linkage to bring together records relating to the same woman; a linkage between that file and the all-causes mortality file of the Registrar General of Ontario; and a linkage with a file containing breast cancer diagnoses from the Ontario Cancer Registry (OCR), a population-based registry of all cancers

diagnosed in Ontario residents. After exclusion of ineligible (i.e. those women diagnosed with breast cancer prior to reproductive surgery; girls under the age of 15 years) or duplicate records, the probabilistic record linkages yielded 524 709 individuals in four procedure-specific subcohorts.

Data were analysed using a person-years approach [9]. Person-years at risk were accumulated until death, a diagnosis of breast cancer, or the end of the study period (31 December 1993), whichever came first. The data in the OCR were used to estimate expected numbers of events. Expected events were calculated by applying 5-year age-, calendar period-, and site-specific cancer rates to person-years accumulated in the cohort, within broad age groupings (15–34, 35–44, 45–54, 55+ years), calendar periods (1979–1983, 1984–1988, 1989–1993) and length of follow-up (less than 1 year, 1 to less than 2 years, 2 to less than 5 years and 5+ years) for each of the surgical procedures. Certain sub-analyses also included age group/follow-up and age group/calendar period cross-classification.

Primary data analysis involved the comparison of the observed to the expected number (O/E) of breast cancers. Four subcohorts were created: tubal ligation only, hysterectomy only, unilateral ovariectomy only and bilateral ovariectomy (with or without hysterectomy). Person-years were calculated separately for each subgroup analysis, and began at the time of the relevant surgical procedure.

It was assumed that the observed number of events arose from a Poisson distribution with mean equal to the expected; *P*-values have been calculated accordingly. Reported *P*-values are two-tailed and represent the probability of a result as extreme as, or more extreme than, the observed number of events.

RESULTS

Table 1 displays the observed and observed/expected ratios for the four subgroups by age at procedure. For all ages combined, there was a protective effect among women who had undergone tubal ligation (O/E = 0.84, $P < 0.001$), hysterectomy (O/E = 0.87, $P < 0.001$) or unilateral ovariectomy (O/E = 0.74, $P < 0.001$). This protective effect was statistically significant within each of the age groups for the hysterectomy subgroup, although there was no trend in risk with age at operation. Women who had had tubal ligation before the age of 45 years or after the age of 54 years were also at decreased risk (although the latter was not statistically significant). Women having this procedure between the ages of 45 and 54 years experienced a non-significant increased risk of breast cancer. The age-specific effects of unilateral ovariectomy followed the same pattern as for hysterectomy, although they were not statistically significant in all age groups. A protective effect of bilateral ovariectomy (with or without hysterectomy) was seen only among women having the surgery under the age of 45 years. For those women having bilateral ovariectomy after the age of 54 years, the risk of breast cancer was increased (O/E = 1.18, $P < 0.001$).

The effect of length of follow-up is explored within cohort subgroups in Table 2. (Initial analyses considered an additional group of patients who had been followed for more than 10 years. No differences were found from the results after 5 years and therefore these categories were collapsed.) No monotonic change in risk was observable with increasing years of follow-up, in any age group (data not shown) or in all ages combined. There was a suggestion, however, of an increased protective effect with longer follow-up for unilateral ovariectomy. The protective effect of hysterectomy was

Table 1. *Observed number and observed/expected (O/E) for breast cancer incidence in a cohort of women undergoing selected surgical procedures, by age at surgical procedure*

Procedure and age at procedure	*n*	Person-years*	Observed	O/E	*P*-value
Tubal ligation only (and other salpingectomy)					
15–34 years	187 820	1 406 851	436	0.77	< 0.001
35–44 years	76 740	525 850	543	0.89	0.007
45–54 years	3392	26 425	59	1.12	0.411
55+ years	471	2966	7	0.72	0.495
Total	268 423	1 962 091	1045	0.84	< 0.001
Hysterectomy only					
15–34 years	28 029	238 418	102	0.80	0.026
35-44 years	59 336	450 773	510	0.85	< 0.001
45–54 years	24 692	187 907	351	0.90	0.044
55+ years	22 636	160 734	464	0.89	0.013
Total	134 693	1 037 831	1427	0.87	< 0.001
Unilateral ovariectomy only					
15–34 years	11 191	89 522	22	0.74	0.187
35–44	6351	45 920	43	0.74	0.044
45–54	2711	18 880	32	0.81	0.259
55+ years	4229	23 977	55	0.70	0.007
Total	24 482	178 299	152	0.74	< 0.001
Bilateral ovariectomy (with or without hysterectomy)					
15–34 years	7361	57 739	19	0.65	0.065
35–44 years	23 256	169 029	157	0.66	< 0.001
45–54	39 239	284 192	616	1.02	0.614
55+ years	27 255	168 080	618	1.18	< 0.001
Total	97 111	679 041	1410	1.01	0.662

*Person-years may not add to total due to rounding.

Table 2. Observed number and observed/expected (O/E) for breast cancer incidence in a cohort of women undergoing selected surgical procedures, by length of follow-up

Procedure and length of follow-up	*n*	Person-years	Observed	O/E	*P*-value
Tubal ligation only (and other salpingectomy)					
< 1 year	268 423	267 493	79	0.89	0.303
1 year– < 2 years	261 067	246 824	99	1.05	0.667
2 years– < 5 years	232 048	577 977	250	0.88	0.044
5+ years	166 013	869 797	617	0.80	< 0.001
Hysterectomy only					
< 1 year	134 693	134 272	121	0.74	< 0.001
1 year– < 2 years	131 980	127 366	166	1.00	1.000
2 years– < 5 years	122 116	322 294	396	0.84	< 0.001
5+ years	92 988	453 899	744	0.89	0.001
Unilateral ovariectomy only					
< 1 year	24 482	24 101	19	0.82	0.465
1 year– < 2 years	23 461	22 392	19	0.86	0.612
2 years– < 5 years	21 369	55 436	45	0.77	0.075
5+ years	15 836	76 370	69	0.68	0.001
Bilateral ovariectomy (with or without hysterectomy)					
< 1 year	97 111	96 098	158	0.95	0.515
1 year– < 2 years	93 423	88 932	155	0.96	0.689
2 years– < 5 years	84 298	215 929	466	1.11	0.029
5+ years	60 613	278 080	631	0.98	0.584

apparent within 1 year of surgery, regardless of age at surgery, although no protective effect was evident at 1 to 2 years of follow-up. An increased protective effect with longer follow-up time was apparent for women undergoing bilateral ovariectomy prior to the age of 35 years (data not shown).

The calendar year in which the surgical procedure occurred appeared not to affect a woman's risk of breast cancer (data not shown). Among all four cohort subgroups, no trend in risk across procedure years was evident. In the earliest time period, however, the protective effect was statistically significant for some age and surgical categories, possibly due to the effect of length of follow-up rather than any factors relating to year of surgery, *per se*. In fact, whilst the small numbers make it difficult to examine, the protective effect of year of procedure disappeared when assessed within categories of age and follow-up time.

DISCUSSION

A number of studies have examined the effect of reproductive surgical procedures on a woman's risk of breast cancer. The protective effect we observed for tubal ligation is consistent with a brief report from South Korea [1], although this effect was not reported in data from the Cancer and Steroid Hormones (CASH) case–control study [3]. Similarly, there are discrepant reports about the relationship between hysterectomy and subsequent risk of breast cancer. Studies which examined the effect of hysterectomy without ovariectomy have generally reported either no association [2, 4], or a protective effect [3, 5]. Our findings provide support for the protective effect of hysterectomy with or without ovariectomy. In contrast to our finding of a protective effect of unilateral ovariectomy, others have not reported a decrease in the risk of breast cancer with this procedure [2, 4, 5]. Whilst these studies were based on relatively small numbers, they indicated a very slight increased risk, if anything.

Data on the effect of bilateral ovariectomy are more numerous and somewhat more consistent. The protective effect of the procedure, if performed before the age of approximately 45 years, observed in our data, is also supported by most researchers [1–6]. This is particularly true for women with longer follow-up, although the effect can be seen even within shorter follow-up durations [3, 4]. Other research also supports our finding of an increased risk of breast cancer when bilateral ovariectomy is performed after the age of 54 years [2, 4]. It may be the effect of having greater exposure to exogenous oestrogen [10] rather than the effect of the surgery *per se*, which increases breast cancer risk in this age group.

The protective effect of ovariectomy at a younger age is probably due to the reduction in ovarian hormone levels [11]. It now appears likely, both from our data and from other recent reports [3, 4], that protection is afforded within a relatively short time after surgery and not only after 10 or more years, as had been thought previously. The other gynaecological operations may alter risk in the same way, although possibly to a lesser extent, given the expected lower reduction in hormone levels that would result from unilateral ovariectomy, hysterectomy or tubal ligation. The literature suggests, in particular, that tubal ligation may impair the blood supply to the ovary and thereby lead to an alteration in the production of oestrogen and progesterone [12, 13]. There is some evidence for this [12, 14] but some researchers have reported no negative impact of tubal ligation on ovarian function [15–17]. Furthermore, literature on ovarian hormone levels following hysterectomy indicates that decreased ovarian function does occur [18], although possibly only temporarily [19], or only if an ovary is removed simultaneously [20].

Certain methodological issues are important to bear in mind when considering our results. The surgical procedures data are based entirely on hospital records and, thus, are not subject to self-reporting errors, as might have occurred in some of the other studies [2, 3, 5]. The outcome data on breast cancer incidence derive from the Ontario Cancer Registry, a population-based registry with upwards of 95% completeness in reporting for breast cancer [21].

Given the data sources, we were unable to obtain data on potential confounding variables. Parity and early menarche are potential confounders of the hysterectomy–breast cancer relationship [22]. Early age at menopause has been associated with a decreased breast cancer risk [23, 24]. It is unclear whether the magnitude of the effect of the reproductive surgery among women under the age of 50 years is equivalent to the degree of protection that natural menopause confers or whether the pronounced reduction in oestrogen levels following surgical menopause (most notably bilateral ovariectomy) provides a greater protection than natural menopause. Controlling for age at menopause would have allowed us to address this issue. Our age stratification, however, did allow us to assess separately the effects for women undergoing these operations most likely during their pre- or postmenopausal years.

Women who have had a bilateral ovariectomy or a hysterectomy without ovariectomy, prior to natural menopause, are more likely to use hormone replacement therapy compared with women who experienced a natural menopause [10]. Furthermore, women who have undergone surgical menopause are more likely to use ovarian hormone therapy (OHT) for more than 5 years and also tend to use oestrogen-only hormone replacement more often [10]. Consideration of these trends in the context of the purported relationship between OHT and breast cancer risk may affect the interpretation of our results. There is no consensus concerning the association between OHT and breast cancer risk, but recent studies suggest that long-term use of OHT is associated with an increased risk of breast cancer [25, 26]. If we had been able to control for OHT use, the protective effect of the operations may have been even greater.

It is possible that the record linkage missed breast cancer cases due to events such as migration out of the province or name changes. We have reported previously that data from Statistics Canada on migration indicate that this is an uncommon event and, thus, its effect would be expected to be very small [7]. As regards name changes, the record linkages all included alternate or previous names, if they were known. Furthermore, other analyses conducted on this cohort showed increased risk for other cancers (notably ovary [7], cervix and thyroid), suggesting that missed links are unlikely to explain our results here.

Finally it is possible that the reason for the surgical procedure, rather than the procedure itself, may affect a woman's breast cancer risk. The most prevalent indications for hysterectomy in Ontario include uterine fibroids, menstrual haemorrhaging, genital prolapse, endometriosis and reproductive cancers [27]. With the exception of endometrial and ovarian cancers (the rarest of these indications), which are weakly associated with breast cancer risk, these diagnoses are not known risk factors for breast cancer. Thus, it is unlikely that failure to control for indication would result in biased risk estimates. Schairer and associates [4] reported that breast cancer risk was not confounded by the main indications for ovariectomy, namely benign ovarian neoplasms, ovarian cysts and endometriosis. Confounding is unlikely both for these reasons and because of the consistency of the protective effect seen across a wide range of procedures, which generally do not have common indications. Thus, we conclude that the data presented here support the hypothesis that reproductive surgical procedures which alter ovarian function may be associated with the risk of breast cancer.

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