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Ovarian cancer in Manitoba: trends in incidence and survival, 1992–2011

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ABSTRACT

Background Because the International Cancer Benchmarking Partnership, in a study of diagnosis years between 1995 and 2007, showed lower-than-expected survival for Manitoba's ovarian cancer patients, we undertook an analysis to describe the features of ovarian cancer diagnosed in Manitoba during a 20-year period. We also determined the most recent trends in survival to see if the previous results were sustained.

Methods In this retrospective cohort study, ovarian cancer cases diagnosed during 1992–2011 were extracted from the Manitoba Cancer Registry. The incidence of ovarian cancer was calculated for the overall group and for age, morphology, residence, treatment, and stage. Trends over time, with a particular focus on changes that might correlate with poor survival, were analyzed. The 1- and 3-year relative survival rates were also calculated.

Results The incidence of ovarian cancer did not vary over time ($p = 0.640$), even when stratified by age or morphology groups. Use of adjuvant chemotherapy decreased ($p = 0.005$) and use of neoadjuvant chemotherapy increased over time ($p = 0.002$). Diagnoses of stage IV cancers declined over time ($p < 0.020$). Trends in incidence did not coincide with previously observed decreases in relative survival.

Conclusions A decline in diagnoses of stage IV ovarian cancer could be responsible for a recent increase in relative survival. However, sample size might have limited power in some analyses, and the previously reported decrease in relative survival might have been due to a random fluctuation in the data. Future efforts will focus on continued monitoring of the patterns of ovarian cancer presentation and outcomes in Manitoba.

Key Words Ovarian cancer, survival, population-based registries

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BACKGROUND

Survival has become a commonly used indicator of cancer control, as demonstrated by recent reports investigating survival worldwide[1,2]. Variations in survival are associated with a variety of factors, including access to appropriate and timely diagnosis and to effective treatment[3], which make survival a useful measure for health care policy evaluation and action. Indeed, as a result of consistent observations of inferior cancer survival in the United Kingdom, a national cancer plan was developed to improve the cancer patient's experience within the health care system, including ways of ensuring that cancer patients are seen in a timely manner[4].

In Canada, survival has become a standard outcome measure in the system performance reports published since 2011[5–8] by the Canadian Partnership Against Cancer, which compare provinces on various statistical measures spanning the cancer control continuum. Canadian provinces have also long participated in international efforts to benchmark the success of their cancer control efforts[1,2]. Notably, the International Cancer Benchmarking Partnership (ICBP) compared cancer survival in a subset of relatively wealthy jurisdictions from the United Kingdom, northern Europe, Australia, and Canada that have similar (public) health care systems, based on cancer cases diagnosed during 1995–2007[9]. Of the four Canadian provinces that participated in the project (British Columbia, Alberta, Manitoba, and Ontario), Manitoba was found to have a 5-year survival for ovarian cancer that was among the poorest measured, despite having fairly good rates of survival for lung and other cancers. In particular, patients diagnosed during 2005–2007 had a 5-year relative survival rate of only 28.8%, which was

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approximately 5 to 15 percentage points lower than the rates in other Canadian jurisdictions.

Given the foregoing findings, the Manitoba Ovarian Cancer Outcomes study group mounted an investigation to explore the reasons for the reported survival deficit, with a particular interest in determining whether the low rates were temporary or evidence of a continuing trend. The present paper articulates the analyses performed on data from the population-based Manitoba Cancer Registry, the province's comprehensive central cancer registry, to address questions about the role of tumour-specific characteristics (stage, morphologic type), patient characteristics (age, place of residence), and treatment over a 20-year period that might have contributed to the difference in survival observed in the ICBP study.

METHODS

Data Sources

Invasive ovarian cancer cases diagnosed between 1 January 1992 and 31 December 2011 were identified through the Manitoba Cancer Registry using the C48.1–C48.8, C56, and C57 codes from the *International Classification of Diseases for Oncology*, which represent the anatomic sites of peritoneum, ovary, fallopian tube, uterine ligaments, and other and unspecified female genital organs. Borderlines cases were excluded. Data extracted from the registry included age at diagnosis, morphology codes, grade, American Joint Committee on Cancer staging (available from 2004 onward), postal code at diagnosis, location of treatment facility, treatment modalities, and death date. Cause of death during the same period was also extracted.

Analyses

Survival and Mortality

Although follow-up for the most recent patient cohort was insufficient to repeat the 5-year survival analyses with updated data, 1- and 3-year relative survival rates, which compare the survival of a cohort with that of the general population[10], were calculated using the cohort approach[11]. All rates were calculated in the SAS software application (version 9.2: SAS Institute, Cary, NC, U.S.A.) using the Ederer method[10] and were age-standardized using international weights[12]. For statistical stability, we grouped the patients into 5 categories spanning 4-year periods (that is, 1992–1995, 1996–1999, ..., 2008–2011). The complementary log–log link function was used to produce 95% confidence limits for the relative survival rates. Survival rates from the 4-year periods, with their 95% confidence limits, were then compared with survival rates during the 20-year study period. Following standard practice and consistent with the ICBP[9] and CONCORD-2[2] publications, ovarian cancer patients between the ages of 15 years and 99 years were included, and patients diagnosed by death certificate or autopsy were excluded.

Ovarian cancer mortality rates over the 20-year study period were analyzed using JoinPoint and were age-standardized to the 1991 Canadian population. Time trends detected by JoinPoint were described as annual percentage changes (APCs), which assume that rates increase or decrease at a constant percentage.

The relationship between overall survival and distance between residence at diagnosis and first treatment facility was analyzed by Cox regression. The last date of follow-up was 31 December 2014. Restricted cubic splines with default knots were used to account for any nonlinearity between the continuous measure of distance and overall survival. The R software application (version 3.2.0: The R Foundation, Vienna, Austria) and the associated rms package were used to run the Cox regression model.

Incidence

Ovarian cancer incidence trends were analyzed for the 20-year study period. Incidence rates were age-standardized to the 1991 Canadian population, and JoinPoint was used for all trend analyses. Incidence trends were also stratified by age (<50 years, 50–74 years, and ≥75 years) and by other factors potentially associated with survival, including morphology (histotypes), geography, and treatment.

Trends in morphology were also analyzed, categorized using standard histotypes [serous carcinoma, mucinous, endometrioid, clear cell, unclassified epithelial, sex cord and germ cell, and other (other classified epithelial–stromal tumours, and miscellaneous and unspecified tumours)] and also using the dichotomous type I and type II system[13]. Type I tumours were defined as low-grade serous carcinoma, low-grade endometrioid, clear cell, and mucinous tumours; type II tumours were defined as high-grade serous carcinoma, high-grade endometrioid, undifferentiated, and other tumours. As is standard practice, sex cord and germ cell were not included in the type I and II classification. Because of low patient numbers for some histotypes, trends were analyzed using 2-year periods.

Incidences for treatment modalities and stage were also analyzed over time. Treatment groups were categorized as surgery only, adjuvant chemotherapy, neoadjuvant chemotherapy (including further adjuvant chemotherapy), chemotherapy only, and no treatment. Treatment categories were defined by the treatments occurring during the first 11 months after diagnosis. Because of small patient numbers in some treatment groups, rates were analyzed using 2-year periods.

Geographic incidence rates were compared with the provincial rates and were stratified into 10-year periods. An inverse gamma distribution was used in SAS to produce 95% confidence limits for low counts[14], which determined whether the geographic incidence rates significantly differed from the provincial rates. The major geographic areas included the province's four predominantly rural regional health authorities (Interlake/Eastern, Northern, Prairie Mountain, and Southern Health–Sante Sud) and the major metropolitan region, Winnipeg, which was further divided into 12 communities.

RESULTS

Between 1992 and 2011, 1931 patients diagnosed with ovarian cancer were identified. Table I presents the cohort characteristics.

TABLE I Characteristics of ovarian cancer patients diagnosed in Manitoba, 1992–2011

Characteristic	1992–1995		1996–1999		2000–2003		2004–2007		2008–2011		Overall	
	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)
Age group												
<50 Years	62	17.32	64	18.45	70	17.37	76	18.49	76	18.44	348	18.02
50–74 Years	193	53.91	177	51.01	213	52.85	215	52.31	230	55.83	1028	53.24
≥75 Years	103	28.77	106	30.55	120	29.78	120	29.20	106	25.73	555	28.74
Morphology												
Clear-cell carcinoma	20	5.59	21	6.05	21	5.21	22	5.35	17	4.13	101	5.23
Endometrioid carcinoma	38	10.61	36	10.37	39	9.68	25	6.08	30	7.28	168	8.70
Mucinous carcinoma	28	7.82	27	7.78	30	7.44	33	8.03	20	4.85	138	7.15
Serous carcinoma	126	35.20	120	34.58	136	33.75	126	30.66	148	35.92	656	33.97
Sex cord and germ cell	13	3.63	10	2.88	12	2.98	14	3.41	16	3.88	65	3.37
Unclassified epithelial	81	22.63	86	24.78	115	28.54	127	30.90	107	25.97	516	26.72
Other tumours	52	14.53	47	13.54	50	12.41	64	15.57	74	17.96	287	14.86
Disease classification												
Type I	69	20.00	70	20.77	87	22.25	77	19.40	57	14.39	360	19.29
Type II	276	80.00	267	79.23	304	77.75	320	80.60	339	85.61	1506	80.71
Treatment												
Adjuvant chemotherapy	178	49.72	183	52.74	163	40.45	142	34.55	161	39.08	827	42.83
Chemotherapy only	28	7.82	35	10.09	77	19.11	72	17.52	46	11.17	258	13.36
Neoadjuvant chemotherapy	11	3.07	10	2.88	40	9.93	59	14.36	83	20.15	203	10.51
Surgery only	82	22.91	56	16.14	63	15.63	65	15.82	46	11.17	312	16.16
No treatment	59	16.48	63	18.16	60	14.89	73	17.76	76	18.45	331	17.14
Stage												
I							83	20.19	95	23.06	178	21.63
II							49	11.92	46	11.17	95	11.54
III							114	27.74	159	38.59	273	33.17
IV							109	26.52	59	14.32	168	20.41
Unknown							56	13.63	53	12.86	109	13.24

Survival and Mortality

We updated our calculation of relative survival to determine if signs of recent improvement were evident. Limited follow-up for the most recent cases necessitated the use of 1- and 3-year relative survival rates. For the entire cohort during the 20-year period, 1-year relative survival was 68.82%, and 3-year relative survival was 44.35%. The period 1992–1995 had a 3-year relative survival rate significantly lower than the 20-year average (37.19%; 95% confidence limits: 31.95%, 42.42%), although the remaining periods were not significantly different from the 20-year average (Table II). Of particular interest, given the ICBP findings, survival for the period 2004–2007 was examined and was not significantly different from the 20-year average. No significant time trends in ovarian cancer mortality rates were found (Figure 1; APC: –0.28; $p = 0.695$).

Despite concerns about the influence of remote and rural geography on patterns, distance between residence at diagnosis and first treatment were not related to overall survival during the 20-year study period (Figure 2, $p = 0.969$); similarly, no relationship to overall survival by diagnosis decade was observed (1992–2001: $p = 0.155$; 2002–2011: $p = 0.388$).

TABLE II Relative survival for ovarian cancer, by period of diagnosis, Manitoba, 1992–2011

Period	1-Year relative survival		3-Year relative survival	
	(%)	95% CL	(%)	95% CL
1992–1995	64.86	59.49, 69.70	37.19	31.95, 42.42
1996–1999	70.96	65.96, 75.37	44.39	38.78, 49.83
2000–2003	72.07	67.37, 76.22	49.12	43.98, 54.04
2004–2007	66.55	61.74, 70.91	43.28	38.29, 48.16
2008–2011	69.64	64.86, 73.90	46.66	41.69, 51.48
Overall	68.82	66.67, 70.86	44.35	42.03, 46.64

CL = confidence limits.

Incidence

The incidence of ovarian cancer varied between 12 and 15 per 100,000 women, but no significant trend in incidence was found over time ($p = 0.640$; Figure 3 presents the modelled values). Also, no significant trends were found when analyses were stratified by age ($p = 0.075$, 0.516, and 0.307 for <50 years, 50–74 years, and ≥75 years respectively) or

by histotype (p = 0.700, 0.090, 0.429, 0.544, 0.920, 0.243, and 0.231 for clear-cell, endometrioid, mucinous, serous carcinoma, sex cord or germ cell, unclassified epithelial, and other ovarian tumours respectively; Figure 4 presents the modelled values).

We observed a nonsignificant trend for type I ovarian cancers (Figure 5), with an APC of 3.02 for 1992–2003 (p = 0.328) and an APC of –6.65 for 2003–2011 (p = 0.161). We also observed a nonsignificant trend for type II ovarian cancers, with an APC of 0.17 for the 20-year period (p = 0.660).

As expected, based on changing standards of practice globally, treatment for ovarian cancer changed over the 20-year period. The rate of surgery as the only treatment decreased significantly over time (APC: –3.26; p = 0.016; Figure 6 presents the modelled values), as did use of adjuvant chemotherapy (APC: –2.27; p = 0.005). Those changes coincided with a significant increase in the use of neoadjuvant chemotherapy (APC: 10.96; p = 0.002), especially beginning in 2002. In addition, use of chemotherapy as the only treatment was observed to significantly increase and then to significantly decrease (APC: 12.79 and –8.96 respectively; p = 0.003 and 0.015

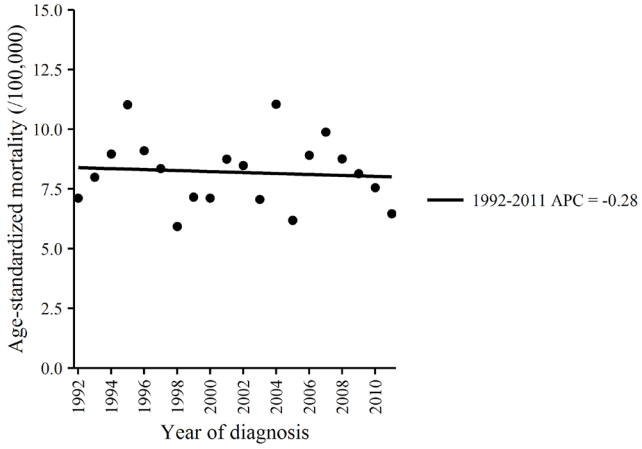

FIGURE 1 Age-standardized ovarian cancer mortality, 1992–2011. APC = annual percentage change.

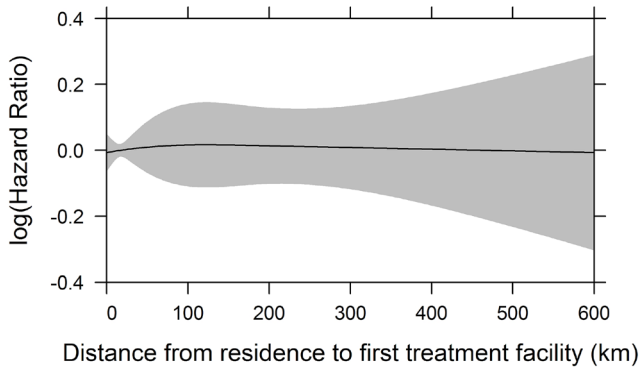

FIGURE 2 Relationship between overall survival and the distance (kilometers) between residence at diagnosis and first treatment facility, 1992–2011.

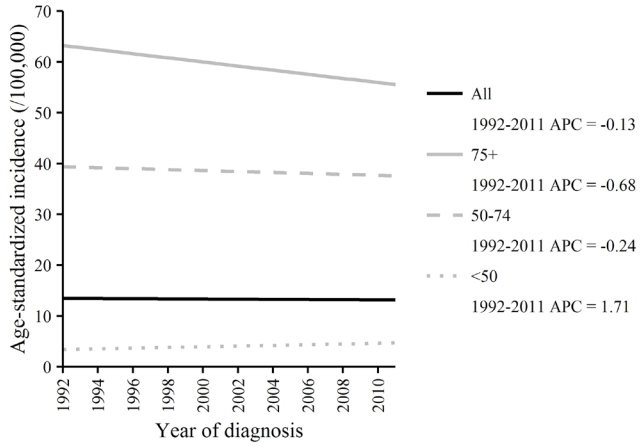

FIGURE 3 Age-standardized incidence of ovarian cancer by age group, 1992–2011. APC = annual percentage change.

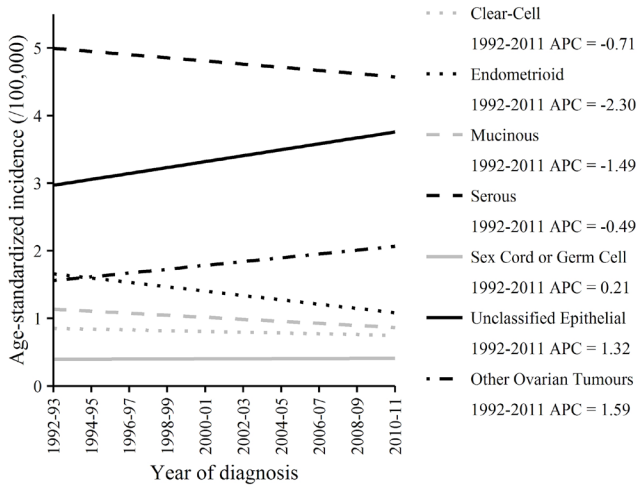

FIGURE 4 Age-standardized incidence of ovarian cancer by morphology, 1992–2011. APC = annual percentage change.

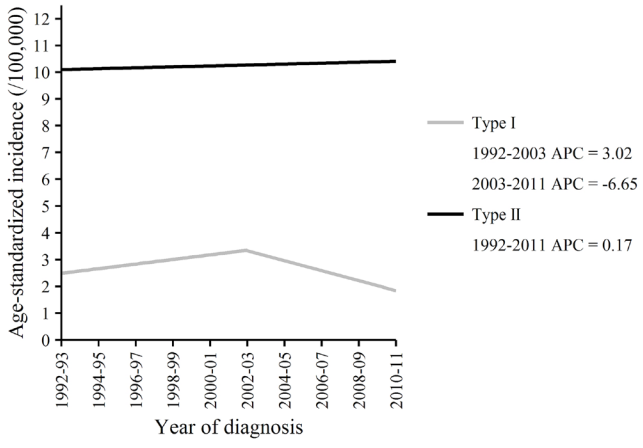

FIGURE 5 Age-standardized incidence of ovarian cancer by disease classification, 1992–2011. APC = annual percentage change.

respectively), with the change occurring in the middle of the 20-year period. However, that effect might have been influenced by the data point representing the rate for 2002–2003, which was higher than the rate in every other period. The rate of patients with ovarian cancer receiving no treatment was unchanged during the 20-year period (APC: 0.67; $p = 0.506$).

No significant time trends were found for rates of stage I or stage II disease during 2004–2011 ($p = 0.437$ and 0.709 respectively; Figure 7 presents modelled values). A significant increase in stage III disease was found after 2007 (APC: 14.57; $p = 0.041$); however, part of that trend might be attributable to the influence of the lower rates observed during 2006–2007. Furthermore, a significant decrease in stage IV disease was found (APC: –12.35; $p = 0.020$), but no significant trend was observed for unknown-stage disease (APC: 10.58 and –54.44; $p = 0.210$ and 0.212 for 2004–2009 and 2009–2011 respectively).

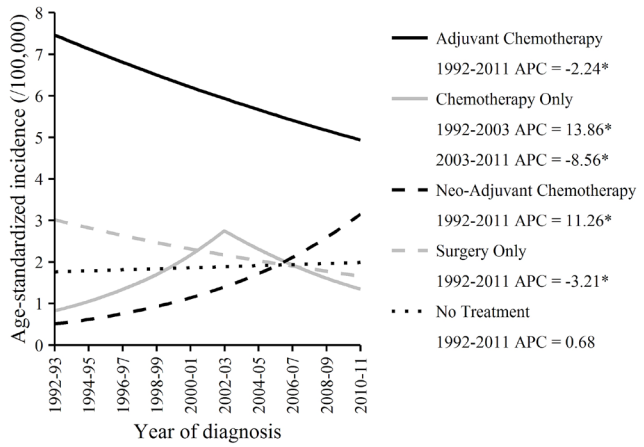

FIGURE 6 Age-standardized incidence of ovarian cancer by treatment, 1992–2011. * Indicates an annual percentage change (APC) significantly different from 0 at the 5% level of significance.

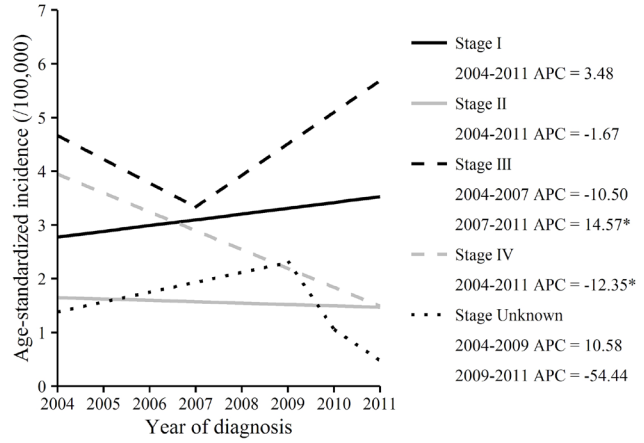

FIGURE 7 Age-standardized incidence of ovarian cancer by American Joint Committee on Cancer staging, 2004–2011. *Indicates an annual percentage change (APC) significantly different from 0 at the 5% level of significance.

Some geographic variations in incidence were found (Figure 8): one Winnipeg community had a significantly higher rate than the provincial rate during 1992–2001 (17.06 per 100,000; 95% confidence limits: 13.34, 21.50; provincial rate: 13.18 per 100,000), and one rural regional health authority had a significantly higher rate than the provincial rate during the 2002–2011 period (18.67 per 100,000; 95% confidence limits: 15.43, 21.91; provincial rate: 13.38 per 100,000).

DISCUSSION

The analysis of relative survival using more recent data was of major interest to us, helping to determine whether the ICBP publication identified a persistent or only a short-term trend. Viewed historically, relative survival for ovarian cancer was relatively stable starting in 1996 (it was significantly lower in 1992–1995 than in later periods). That trend likely corresponds to the publication of the GOG-111 trial[15] and the introduction of cisplatin–paclitaxel combination chemotherapy into modern practice. Relative survival for the period 2004–2007 was indeed lower than for other periods. That was the period reflected in the ICBP publication, but we found that, immediately afterward, Manitoba's relative survival rate for ovarian cancer was substantially higher. Although the change in relative survival over time did not correlate with changes in treatment, the decrease in relative survival does correlate with a higher rate of stage IV ovarian cancer during 2004–2007, which continued to decline over time—and coincides with the recent improvements in survival. Unfortunately, stage data were not available before 2004 to further elucidate the trends in outcome. The decrease in stage IV cases could be related to factors not collected by the Manitoba Cancer Registry, such as time to diagnosis or treatment.

No significant trends in the overall incidence of ovarian cancer over time were found during 1992–2011. Although no significant trends were found when the data were stratified by age, a nonsignificant decrease for patients

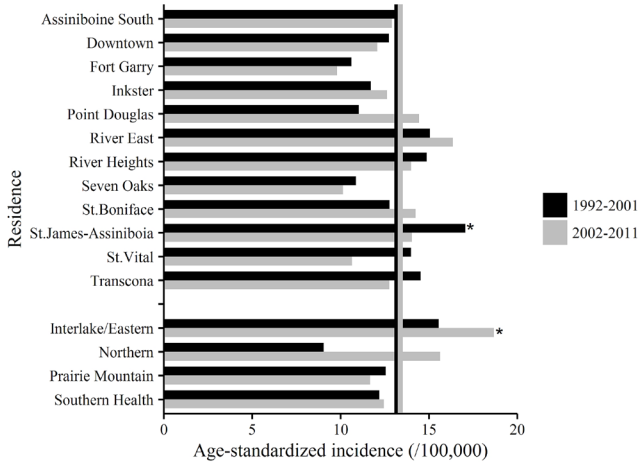

FIGURE 8 Age-standardized incidence of ovarian cancer by residence and 10-year period, 1992–2011. *Indicates a significant difference from provincial rate at the 5% level of significance.

50 years of age and older and a near-significant increase in incidence for those less than 50 years of age were observed. Despite the nonsignificant trend for older women in the analysis (likely because of the small sample size), recent publications have found a change in incidence for women 50 years of age and older starting in the early to mid-2000s[16,17]. The decrease in incidence in England was postulated to be a result of the widespread availability of oral contraceptives that began in the 1960s[16]. On the other hand, after analyzing 42 population-based cancer registries in the United States, Yang *et al.*[17] suggested a possible link between the decrease in ovarian cancer incidence during 2003–2008 and the publication of the U.S. Women's Health Initiative study in which the benefits of hormone replacement therapy were questioned[18]. Indeed, a recent meta-analysis found that, compared with non-users of hormone replacement therapy, current users had a higher risk of developing ovarian cancer[19].

Although nonsignificant (again likely because of the small numbers), our trends in prognostic characteristics (morphology and stage) were interesting. Although we did not observe an increase in serous and a decrease in unclassified epithelial cancers after 2002 as was found in England[16], incidence by stage did vary over time. Specifically, an increase in stage III (after 2007) and a decrease in stage IV ovarian cancers occurred. Those changes could be an important factor in interpreting the decrease in the relative survival rates found in the ICBP publication[9], which did not present findings by stage.

During the 20-year period, trends in treatment rates were observed: decreases in surgery alone and in adjuvant chemotherapy were found. An increase in neoadjuvant chemotherapy was also found, but that treatment remained less common than adjuvant chemotherapy. The trend was especially evident after 2002, which might correlate with publications related to the neoadjuvant chemotherapy trial by Vergote *et al.*[20], who had been actively accruing patients for their study between 1998 and 2006.

We note that, although some geographic variation in incidence was found, incidence rates for only two geographic regions differed significantly from the provincial rate, and those differences did not occur in the same time period. A likely explanation is that, because of the number of comparisons, one or both significant differences could be random. No relationship between survival and distance from residence at diagnosis to first treatment facility could be found, providing evidence of equity in treatment access regardless of residence, which is important, given that some Manitobans live very far (up to 1100 km) from Winnipeg (where all Manitoba gynecologic oncologists are located). However, geographic equity will continue to be monitored to ensure that conclusions are based on adequate power: Note that an estimated 55% of residents live in Winnipeg, and few patients with ovarian cancer live far from Winnipeg (10% of such patients lived an estimated 180 km and 2.5% lived an estimated 450 km from Winnipeg).

Although the present analysis was motivated by concerns about survival, it is noteworthy that no time trend in mortality was found. Although cause of death might suffer from issues of accuracy, it is unlikely that any bias would have occurred over time.

CONCLUSIONS

A strength of the present study is the quality of the Manitoba Cancer Registry, which consistently obtains gold certification by the North American Association of Central Cancer Registries[21]. In the ICBP analysis, Alberta was the only other province that had also consistently obtained gold certification, and they too showed lower survival rates than British Columbia and Ontario for 2 of 3 periods in the ICBP publication.

In summary, the availability of high-quality population-based cancer registry data allowed us to investigate a variety of factors potentially associated with previously observed rates of lower-than-expected ovarian cancer survival. None of the investigated factors (age, histologic type, distance from treatment centres, treatment types, or stage) were clearly associated with the survival patterns, which established the need for the use of more resource-intensive data collection (that is, chart review) to further evaluate additional clinical factors, such as those surrounding timely access to specialist care. That work is currently underway; however, the available data also supported a timely updated survival analysis of a more recent cohort of ovarian cancer patients diagnosed in Manitoba. The results suggest improvements in survival and the possibility that any deficits in survival reported in the original ICBP publication for the period 2005–2007 have been resolved, given that the 1- and 3-year survival rates have returned to usual levels.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: AA and DT report grants from the CancerCare Manitoba Foundation and the Canadian Partnership Against Cancer. AA also reports being a site principal investigator for the NCIC CX.5 trial, the JAVELIN Ovarian 200 trial, and the Array BioPharma MILO study, and receiving speaking honoraria from AstraZeneca, Merck, Roche, and Sanofi. The remaining authors have no conflicts of interest to declare.

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