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Overestimated risk of second primary malignancies in ovarian cancer patients

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Abstract

Registry-based cohort studies have established an increased risk of developing second primary malignancies (SPM) in patients with a primary ovarian cancer. In order to examine the accuracy of cancer registration with emphasis on registration of SPM, 344 women with ovarian cancer and 379 subsequent SPM, registered between 1958 and 1992 in the Stockholm-Gotland Cancer Registry (SGCR), a division of the Swedish Cancer Registry (SCR), were investigated. Complete records including pathology reports were examined and an additional histopathological evaluation was conducted for a sample of the group. The results revealed that 28 diagnoses of SPM were incorrectly registered (14 cases were misdiagnosed SPM of the gastrointestinal tract, mainly colon and rectum) and 34 women (with 38 SPM) were incorrectly registered with ovarian cancer. Recalculations of the risk of a subsequent cancer were performed on the basis of these findings and the results suggest an overestimation of the risk of developing SPM. Inferences of these findings to other primary sites of multiple malignancies should be made with caution and further studies are needed.

Keywords: Ovarian cancer; Second primary malignancies; Misclassification; Cancer registration

1. Introduction

Since the entity of multiple malignancies in the same individual was first described at the end of the 19th century the subject has been studied by several investigators [1–4]. Studies of these second primary malignancies (SPM) are important and could provide clues to the understanding of cancer aetiology in several aspects. Studies of SPM have made an essential contribution to the discovery of hereditary cancer syndromes, e.g. the Li–Fraumeni syndrome [5], hereditary nonpolyposis colon cancer [6,7], hereditary breast and ovarian cancer [8] and hereditary malignant melanoma [9]. Increasing cure rates for several types of cancer have revealed the problem of treatment-induced cancers, e.g. where SPM occurs after exposure to radio- and/or chemotherapy [10–13]. Studies of SPM have also revealed common aetiological factors, such as smoking and hormones, both strongly associated with specific sites of cancer [14–16].

The accuracy of cancer registration is essential when studying SPM. Numerous misclassifications, e.g. when metastasis or relapse of the primary cancer is registered as SPM, or the opposite, a true SPM is registered as relapse of the first primary malignancy, are likely to affect the incidence and thus any risk estimates. The importance of high-quality data has been underlined in several studies [17–20].

2. Patients and methods

A cohort of women with ovarian cancer and one or more SPM registered in the Stockholm-Gotland Cancer Register (SGCR), a regional division of the Swedish Cancer Register (SCR), was chosen for the study in

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order to examine the impact of misclassification on the reliability of SPM-registration. An overall increased risk of SPM amongst these women (standardised incidence ratio (SIR) 1.49; 95% confidence interval (CI) 1.34–1.64) has previously been described [21]. Significantly increased risks of leukaemia, as well as cancers of the gastrointestinal tract (mainly cancer of the colon and rectum), breast, uterine corpus and bladder were found. These findings were in agreement with previous studies [22–26].

The SCR receives notification of newly diagnosed malignancies and it is mandatory not only for clinicians but also for pathologists and cytologists to report these malignancies to the SCR. Most diagnosed cases are thus reported from at least two independent sources and more than 96% of all solid cancers will be found in the register [27]. It is also obligatory to make corrections if the initial diagnosis turns out to be wrong. SCR collects information on name, personal identification number, diagnosis, date of diagnosis and date of death, but includes no information concerning treatment, stage or histopathology. The tumours are coded in accordance with ICD7 [28].

The coincidence of two or more malignant diseases in the same person is known under several names: multiple primary cancers, secondary malignant neoplasms, or second primary malignancies (SPM), the latter abbreviation will be used in this paper. Definitions of SPM have changed over the years and among different cancer registries. Today, the most widely used definition is that proposed by the International Association of Cancer Registries (IACR) and the International Agency for Cancer Research (IARC) [29]. The principles are that each registered diagnosis of cancer must originate in one site or tissue and that the possibility of relapse or metastasis from a previous cancer is excluded. Furthermore, the recognition of two or more primary cancers does not depend on time and only one tumour per organ is accepted, except when there is a difference in morphology.

The SCR follows the principles of the IARC with some exceptions stated in governmental regulations concerning certain types of benign tumours. Precancerous lesions, classified as cancer *in situ* or atypical epithelial proliferations are also registered, but coded as benign and not included among SPM in this study.

The SGCR is a regional division of the SCR, both established in 1958. In 1994, a total of 1.75 million people (51% women) lived in the area covered by SGCR. Patients with a primary diagnosis of ovarian cancer and one or more subsequent SPM were included in the present study. Patients older than 80 years of age at primary diagnosis and cancer diagnosed at autopsy were not included.

A total of 5060 patients with ovarian cancer were reported to the SGCR during the period 1958–1992. Among them, 344 were diagnosed with a total of 379 SPM. The care of patients with gynaecological cancers in SGCR area are centralised to the Department of Gynaecological Oncology at Radiumhemmet, Karolinska University Hospital, Stockholm, which gives access to clinical data of almost all diagnosed patients. Despite that, 10 patients with 10 diagnoses of SPM, could not be included in the study since their case records were not found. These SPM, as well as their ovarian cancer diagnoses, were assumed to be correctly registered.

The diagnoses notified in the SGCR were compared with hospital records, including primary pathology reports and the pathological re-examination routinely made by tumour pathologists when patients were admitted to Radiumhemmet, Karolinska University Hospital. To establish the reliability of cancer registration further, histopathological slides from 25 ovarian cancers and 76 SPM were randomly collected for a second re-examination by an experienced tumour pathologist.

The false registered SPM were divided into two major categories: incorrect diagnosis of ovarian cancer and incorrect diagnosis of SPM and each major category was subdivided into five groups (Table 1).

3. Results

According to existing records and the second histopathological evaluation in this study 66 SPM (17%) were incorrectly registered, 28 due to incorrectly registered SPM and 38 due to incorrectly registered diagnoses of ovarian cancer in 34 women (Table 1).

3.1. Incorrect registration of ovarian cancer

In category 1, where the diagnoses of ovarian cancer were incorrect, 20 patients, with 23 SPM (35%), turned out to be diagnosed with benign ovarian disorders (Table 1: 1a). In 12 of those cases (with 13 SPM) the primary diagnoses were thecoma, a benign ovarian tumour registered in the SGCR according to Swedish legislation [25] and in 8 cases (with 10 SPM), the tumour registered as ovarian cancer turned out be of benign origin, but the corrections were never reported to the SGCR.

In 12 cases (18%) the records revealed that the initial diagnosis of ovarian cancer was incorrect, since the tumours were stated to be metastases of other malignancies, mistakenly registered as ovarian cancer (Table 1: 1b); 9 were metastases of the gastrointestinal tract; 1 was of pulmonary origin and 2 were metastases of sarcomas not of ovarian origin. Three SPM (5%) occurred in 2 patients where the registered diagnoses of ovarian cancer, in fact were relapses in the same disease, diagnosed before the register was set up (Table 1: 1e).

Table 1
Distribution of 66 incorrectly registered SPM out of 379 re-evaluated tumours

Category	No. of SPM (%)	No. of errors (%)	
		1958–1975	1976–1992
1a Benign ovarian tumour	23 (35)	13	10
(No. of thecoma)	(13)	(3)	(10)
1b Metastasis of non-ovarian cancer	12 (18)	8	4
1c Primary ovarian cancer found to be benign[a]	0 (0)	0	0
1d Primary ovarian cancer metastasis of another neoplasm[a]	0 (0)	0	0
1e Other causes of misdiagnosed OC	3 (5)	3	0
All of category 1	38 (58)	24	14
2a SPM stated to be benign	5 (8)	0	5
2b SPM metastasis or relapse in OC	19 (29)	12	7
2c SPM found to be benign[a]	2 (3)	1	1
2d SPM metastasis or relapse in OC[a]	1 (2)	0	1
2e Other causes of misdiagnosed SPM	1 (2)	1	0
All of category 2	28 (42)	14	14
All categories	66[b] (100)	38	28
All SPM (%)	379 (17)	98 (39)	281 (10)

Category 1, SPM in cases of incorrectly registered ovarian cancer (OC). Category 2, incorrectly registered SPM.
[a] Misregistrations revealed at second pathological re-evaluation performed in this study.
[b] 63 of 66 errors in registration due to lack of forwarding corrected diagnoses to the cancer registry.

The errors in registration of SPM in all 38 (58%) after incorrectly registered ovarian cancers were registered as cancers of the following sites: stomach ($n=3$), colon ($n=5$), liver ($n=2$), pancreas ($n=2$), lung ($n=1$), breast ($n=7$), uterus ($n=2$), kidney ($n=1$), bladder ($n=2$), melanoma ($n=1$), lymphoma ($n=2$), myeloma ($n=2$), sarcoma not of ovarian origin ($n=2$), gall bladder ($n=2$), unspecified generalised cancer ($n=3$) and adenoma of the parathyroid gland ($n=1$).

3.2. Incorrect diagnosis of SPM

According to available records 5 SPM (8%) (of the cervix, vagina, colon and two skin cancers) were stated as '*in situ* cancers' or 'atypical cells' (Table 1: 2a), whilst 19 SPM (29%) were metastasis from, or relapses in, ovarian cancer ($n=18$) or other SPM ($n=1$) (Table 1: 2b). The latter was a patient registered with two SPM, cancer of the colon and the stomach, the tumour in the stomach turned out to be a relapse in colon cancer.

Additionally one SPM was found incorrectly registered, since the patient died 2 years before registration of the SPM, and there were no notifications in the records suggesting any kind of SPM (Table 1: 2e).

3.2.1. Pathological re-evaluation

In order to further evaluate the validity of SGCR, randomly selected histopathological slides from the original tissue samples for this group of women were requested from the pathological laboratories in the area of SGCR. Out of a requested 47 ovarian cancers and 121 SPM, 25 (53%) and 76 (63%), respectively, were available for re-evaluation by an experienced tumour pathologist. All diagnoses of ovarian cancer were found to be correct (Table 1: 1c and 1d), whilst 3 cases of SPM (4%) were incorrectly diagnosed (Table 1: 2c and 2d): one SPM of the rectum and one of the cervix were revealed to be '*in situ*', and one SPM of the small intestine was a relapse in ovarian cancer.

Of 28 incorrectly registered SPM (42%), 14 were registered as gastrointestinal tumours, i.e. cancer of the stomach ($n=1$), small intestine ($n=3$), colon ($n=6$), rectum ($n=2$) and pancreas ($n=2$). Additional findings were cancer of the breast ($n=2$), uterus ($n=3$), uterine cervix ($n=3$), vagina ($n=1$), kidney ($n=1$), skin ($n=2$), lymphoma ($n=1$) and one undefined tumour (ICD-7 = 199).

According to a previous study on the same cohort of women with ovarian cancer, the overall risk of developing a subsequent malignancy was increased (SIR 1.49; 95% CI 1.34–1.64, $n=379$) [21]. Significantly increased risk factors were established for cancer of the gastrointestinal tract (SIR 1.64; 95% CI 1.34–1.96, $n=112$), cancer of the colon (SIR 2.53; 95% CI 1.89–3.31 $n=53$), rectum (SIR 1.73; 95% CI 1.02–2.73, $n=18$), uterine corpus (SIR 2.20; 95% CI 1.49–3.12, $n=31$), breast (SIR 1.41; 95% CI 1.14–1.75, $n=89$), bladder (SIR 2.74; 95% CI 1.64–4.19, $n=21$) and for leukaemia (SIR 6.79; 95% CI 3.80–11.19, $n=15$). This contribution of misregistered SPM to the originally found numbers of SPM in sites with increased risk is graphically illustrated in Fig. 1.

The originally observed numbers of 379 SPM were reduced by 66 incorrectly registered cases. Gastrointestinal cancers ($n=112$) were reduced by 27, colon

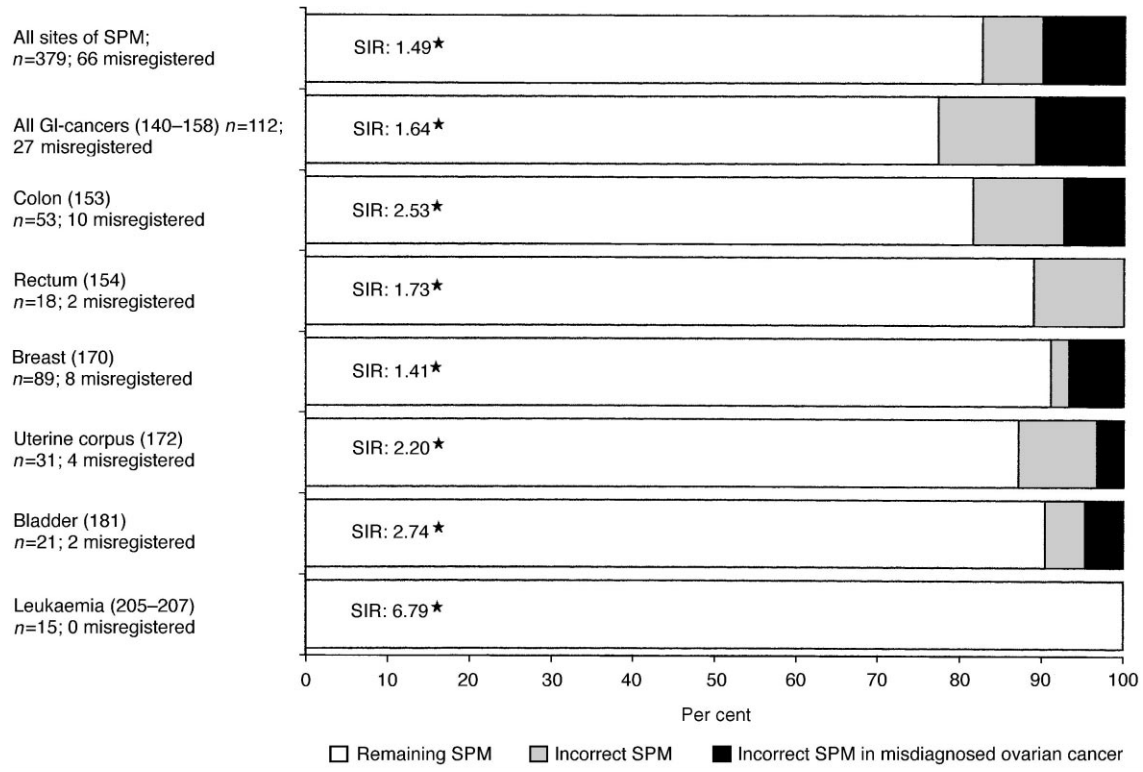

Fig. 1. Contribution of misdiagnosed SPM to total number of SPM in sites (ICD7) with previously established and statistically significant increase of risk. *SIR, standardised incidence ratio before corrections with 95% confidence interval.

($n=53$) by 10, rectum ($n=18$) by 2, breast ($n=89$) by 9, uterine corpus ($n=31$) by 4, bladder ($n=21$) by 2, and for leukaemia no misregistered SPM was found.

Investigation of the temporal pattern of incorrect registration revealed that the highest rate of misregistrations, 39% ($n=38$ out of 98), appeared during the earlier year of Swedish cancer registration (1958–1975), compared with 10% ($n=26$ out of 281) in the subsequent period 1976–1992 (Table 1).

Using the findings in the present study previous risk estimates were recalculated to examine how the new information altered the results. The influence on the expected number of cases by the decreased numbers of SPM was assumed to be negligible, since the expected numbers are calculated on nation-based cancer incidence. To estimate the influence of the misdiagnosed cases of ovarian cancer, we assumed that the same proportion of errors in diagnosis occurred in the cohort of women with ovarian cancer only, as in the group with ovarian cancer and a subsequent SPM with the exception of the 12 cases where the ovarian cancer turned out to be a metastasis of the SPM. Since the error is dependent on the existence of a second malignancy, this type of misdiagnosing could not occur in the group of women with ovarian cancer only.

From this it follows that the correction factor for estimating the correct number of ovarian cancer diagnosis could be calculated as $1-((34-12)/344)=0.94$ (1 minus the number of misdiagnosed ovarian cancers, minus the number of not representative misdiagnoses in relation to the total number of ovarian cancers in the study). 94% of 5060 ovarian cancers could be assumed to be correct and the originally calculated numbers of expected new malignancies among them should then be corrected by a factor of 0.94.

Recalculation of SIR, based on the findings in the present study and the decreased numbers of expected new malignancies, showed that the actual risk seems to be smaller than previously described (Table 2). Corrected overall risk of SPM after ovarian cancer turned out to be 1.31 (95% CI 1.16–1.45) and the risk of SPM of the gastrointestinal tract 1.32 (95% CI 1.06–1.64). Recalculations of SIR by individual sites gave the following results: colon 2.18 (95% CI 1.58–2.94), rectum 1.64 (95% CI 0.94–2.66), uterine corpus 2.04 (95% CI 1.34–2.97), breast 1.37 (95% CI 1.07–1.66), and bladder 2.64 (95% CI 1.59–4.12). For leukaemia we noticed an increased risk, SIR 7.21 (95% CI 4.04–11.89) after recalculation, since no incorrect diagnosis of leukaemia was found.

4. Discussion

The accuracy of cancer registration is of crucial importance for epidemiological studies of cancer inci-

Table 2
Observed and expected numbers of cancer, standardised incidence ratio (SIR) and 95% confidence interval (CI) before and after adjusting for the incorrectly diagnosed ovarian cancer and SPM

	Before				After			
Site	Observed	Expected	SIR	95% CI	Observed	Expected	SIR	95% CI
All GI-tract	112	68.29	1.64	1.34–1.96	85	64.19	1.32	1.06–1.64
Colon	53	20.95	2.53	1.89–3.31	43	19.69	2.18	1.58–2.94
Rectum	18	10.40	1.73	1.02–2.73	16	9.78	1.64	0.94–2.66
Breast	89	63.12	1.41	1.14–1.75	81	59.33	1.37	1.07–1.66
Uterus	31	14.09	2.20	1.49–3.12	27	13.24	2.04	1.34–2.97
Bladder	21	7.66	2.74	1.69–4.19	19	7.20	2.64	1.59–4.12
Leukaemia	15	2.21	6.79	3.80–11.19	15	2.08	7.21	4.04–11.89
Total[a]	379	254.36	1.49	1.34–1.64	313	239.10	1.31	1.16–1.45

GI, gastrointestinal.
[a] All sites of SPM included.

dence and risk calculations. In studies of SPM after any primary cancer, validity of registration is of no less importance. The possibility to study hereditary cancer syndromes, common aetiology and possible correlations between therapy and the development of SPM are based on the assumption that the cancer registries are reliable. Previous investigators have demonstrated a high quality of data of the SCR [22, 27].

The findings of 28 incorrectly registered SPM and 34 incorrectly registered cases (38 SPM) of ovarian cancer in this cohort of women suggest that the previously proven risk of SPM was overestimated. This overestimation was most pronounced for SPM of the colon and the gastrointestinal tract as a whole, whilst the increased risk of developing cancer of the rectum was no longer statistically significant. Despite this reduction in SIR, the evidence for an actually increased risk of developing SPM after ovarian cancer in general, and cancer of the colon, breast, uterine corpus, bladder as well as leukaemia in particular, must be considered even stronger than before, since the risk in these sites remained significantly increased. Although there are several ways to present the findings in this study, in order to re-calculate the risk of SPM, the approach chosen is more likely to be conservative and rather underestimate the risk than the opposite.

The vast majority of errors in SPM-registrations (63 out of 66) were due to the fact that corrections of diagnoses were limited to the records and never forwarded to the cancer registry. The major part of these misregistrations were made during the first decades of cancer registration in Sweden, which suggest an improvement over time, implying that the accuracy of cancer registration will be better in the future. The findings also imply that the registrations of benign tumours (thecoma) in cancer registries, makes a small, but not negligible, contribution to the risk of SPM among patients with ovarian cancer (13 SPM in 12 patients).

The histopathological re-evaluation of SPM diagnosis by an experienced tumour pathologist revealed that 3 (4%) out of 76 were incorrect, indicating that the number of incorrect SPM in the cohort could be even higher, if all histopathological slides were to be re-examined. 2 out of 3 were of gastrointestinal origin, which further stresses the problems of correct diagnosis at this site.

It is an open question if these findings concerning SPM after ovarian cancer in Swedish women are applicable to the findings of other investigators [21–25]. It is also most uncertain if these findings are applicable to other sites of first primary malignancies, known to have an increased risk of developing subsequent malignancies. Inferences should be made with caution and the results suggest the need for further studies, since ovarian cancer, as primary site, might be particularly problematic when studying SPM.

The results also imply that, when studying second primary malignancies, cohort studies using data from cancer registries might not be the optimal method in assessing risk, and instead case–control studies might be preferable. The results also indicate that the high quality of the SCR, as shown in previous studies [27], could be further improved, if diagnostic reconsideration made by clinicians and pathologists are reported to the SCR to the same extent as the primary diagnosis.

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