

Original Article



Incidence and predictors of peritoneal metastases of gynecological origin: a population-based study in the Netherlands

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ABSTRACT

Objective: Peritoneal metastases (PM) are a challenge in gynecological cancers, but its appearance has never been described in a population-based study. Therefore, we describe the incidence of PM and identify predictors that increase the probability of peritoneal spread.

Methods: All ovarian, endometrial and cervical cancer patients diagnosed in the Netherlands between 1989 and 2015 were identified from the Netherlands Cancer Registry and stratified for PM. Crude and age-adjusted incidence over time was calculated. Independent predictors for PM were identified using uni- and multivariable analyses.

Results: The 94,981 patients were diagnosed with ovarian, endometrial or cervical cancer and respectively 61%, 2% and 1% presented with PM. Predictors for PM in ovarian cancer were: age between 50 and 74 years (odds ratio [OR]=1.19; 95% confidence interval [CI]=1.08–1.32), other distant metastases (OR=1.25; 95% CI=1.10–1.41), poor differentiation grade (OR=2.00; 95% CI=1.73–2.32) and serous histology. Predictors in endometrial cancer were lymph node metastases (OR=2.32; 95% CI=1.65–3.26), other distant metastases (OR=1.38; 95% CI=1.08–1.77), high-grade tumors (OR=1.95; 95% CI=1.38–2.76) and clear cell (OR=1.49; 95% CI=1.04–2.13) or serous histology (OR=2.71; 95% CI=2.15–3.42). In cervical cancer, the risk is higher in adenocarcinoma than in squamous cell carcinoma (OR=4.92; 95% CI=3.11–7.79).

Conclusion: PM are frequently seen in patients with ovarian cancer. In endometrial and cervical cancer PM are rare. Histological subtype was the strongest predictive factor for PM in all 3 cancers. Better understanding of predictive factors for PM and thus the biological behavior is of paramount importance.

Keywords: Peritoneal Neoplasms; Ovarian Neoplasms; Endometrial Neoplasms; Uterine Cervical Neoplasms; Incidence; Epidemiology

Presentation

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: V.A.A., B.D., B.L.; Data curation: T.M., V.D.A.M.; Formal analysis: T.M., R.K., B.L.; Methodology: T.M., R.K., B.L.; Software: T.M., R.K., B.L.; Validation: V.D.A.M.; Visualization: B.L.; Writing - original draft: B.L.; Writing - review & editing: T.M., V.D.A.M., B.D., R.K., D.H.I., V.A.A.

INTRODUCTION

In 2015, over 4,000 women in the Netherlands were diagnosed with ovarian, endometrial or cervical cancer [1]. Ovarian cancer is known to present with peritoneal metastases (PM) already at the time of diagnosis in a considerable number of patients. Due to the advanced stage at diagnosis it is associated with an impaired clinical outcome [2-4]: the overall 5-year survival rate is less than 30% [3-6]. In cervical and endometrial cancer, PM are less often reported [7,8].

A better understanding of the biological behavior of gynecological cancers is of paramount importance to improve treatment strategies. Analyzing the pattern of metastasis in gynecological cancers and the predictive factors for having PM can contribute to the clarification of this behavior. Until recently, gynecological cancer patients were treated according to the origin of the gynecological tumor, independent of other factors like histological type. Nowadays more attention is given to the differences between the histological subtypes of gynecological cancer and the pattern of metastases [9-11]. The histological subtype is expected to be a predictor for the occurrence of PM [12]. Nevertheless, more knowledge about predictive factors on PM is necessary. This is especially the case since promising therapeutic modalities are upcoming.

To the best of our knowledge, no population-based studies on the incidence of PM in gynecological cancers have been conducted. In addition, predictive patient- and tumor characteristics for the development of PM of gynecological origin are not yet studied on a large scale. Therefore, we describe the incidence of PM in gynecological cancers and identify predictors that increase the probability of peritoneal spread, so we can contribute to an increasing clinical guidance into a more targeted treatment strategy for patients with gynecological cancers.

MATERIALS AND METHODS

1. Data collection

We conducted a retrospective study. All consecutive patients with primary ovarian (C56, C57, C48), endometrial (C54, C55) and cervical (C53) cancer diagnosed between 1989 and 2015 were identified from the Netherlands Cancer Registry (NCR) [13]. Registration in the NCR takes place based on notification of newly diagnosed malignancies in the Netherlands by the automated nationwide pathology archive (Pathological Anatomical National Automated Archive [PALGA]). Specially trained administrators of the NCR routinely extract information on patients and tumor characteristics from the medical records. Completeness of the NCR is estimated to be over 95% [14].

The data contained patient characteristics, such as date of diagnosis and age at diagnosis. Socio-economic status was based on a patient's postal area according to the Netherlands Institute for Social Research [15]. A medical history of other malignant (non-) gynecological tumors was derived from the NCR.

The International Federation of Gynecology and Obstetrics (FIGO) stage was derived from the tumor, node, and metastasis (TNM) staging system and was based on postoperative findings for ovarian cancer and endometrial cancer. In cervical cancer patients, FIGO was

based on clinical staging, using all available medical information of the patients as accurately as possible including imaging techniques, scopies and biopsies. Moreover, if patients underwent neoadjuvant chemotherapy, stage was based on clinical findings again including imaging, scopies and biopsies in order to avoid downstaging in case of good response. Lymph node involvement and distant metastases were identified. In case patients did not undergo surgical treatment, FIGO stage, lymph node involvement and distant metastases were based on clinical information (such as imaging techniques). As such, this was not in all cases histologically confirmed. Type of histology was classified into groups based on the primary site of the tumor.

2. Statistical analyses

Patients were distributed among period groups according to the year of diagnosis (1989–1994, 1995–2000, 2001–2005, 2005–2010, 2011–2015) and into age groups (18–49 years, 50–74 years, >75 years). Descriptive statistics were used to provide an overview of all patients with gynecological cancer. Early stage ovarian (FIGO stage I–IIa), endometrial (FIGO stage I–II) and cervical (FIGO stage I–II) cancer patients were excluded from further analyses, as by definition, they could not develop PM. Ovarian cancer patients with an unknown FIGO stage were included, as TNM was not registered within the NCR for primary peritoneal cancers until 2010. Endometrial and cervical cancer patients with an unknown FIGO stage were excluded. Crude and European standardized (European standardized rate) incidence rates of ovarian, endometrial and cervical cancer patients with PM were calculated. Since registration in the NCR expanded in 2005 for the localization of metastases, a subgroup analysis regarding age-adjusted incidence rates between 2005 and 2015 was conducted. Independent predictors for the occurrence of PM were identified using the univariable and multivariable logistic regression analyses. Only characteristics that were significant in univariable analyses were included in the multivariable analyses. A p-value <0.05 was considered statistically significant for all analyses. Statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, USA).

3. Ethical approval

Local ethical approval was not applicable, since this study concerns retrospective population-based data, provided by the NCR. The medical ethical committee of the NCR assessed, approved and provided the required dataset for this study.

RESULTS

Between 1989 and 2015, in total 94,981 patients were diagnosed with ovarian (n=33,366), endometrial (n=42,333) and cervical cancer (n=19,282) in the Netherlands (**Fig. 1, Table 1**). The vast majority of PM (96%) was found in patients with ovarian cancer.

1. Ovarian cancer with PM

Sixty-one percent (n=20,401) of all ovarian cancer patients presented with PM. The mean age at diagnosis was 65.7 years (**Table 2**). The 89% of advanced stage ovarian cancer patients had PM without other metastases. The histology in the majority of patients was serous adenocarcinoma (51%) or adenocarcinoma not otherwise specified (NOS) (28%). An increase in crude incidence of PM was seen over the time (**Fig. 2A**). The age-adjusted incidence between 1989 and 2015 however was stable (p=0.79, **Fig. 2B**). The conducted subgroup analysis of incidence rates between 2005 and 2015 that was performed because of a change

Incidence and predictors of peritoneal metastases

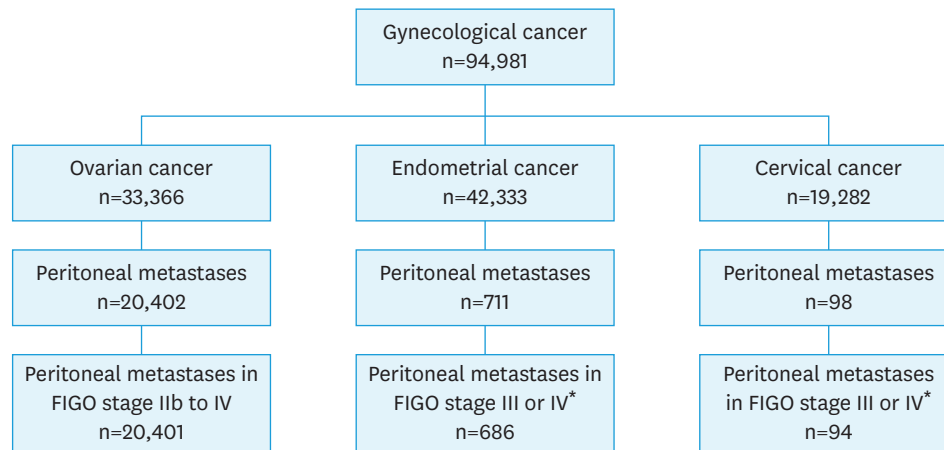


Fig. 1. Flowchart of patients diagnosed with gynecological cancer between 1995 and 2015 in the Netherlands, according to NCR data. FIGO, International Federation of Gynecology and Obstetrics; NCR, Netherlands Cancer Registry. *Patients with an unknown FIGO stage are excluded.

Table 1. Patient and tumor characteristics of all patients diagnosed with gynecological cancer between 1989 and 2015 in the Netherlands (n=94,981)

Characteristics	Ovarian cancer (n=33,366)	Endometrial cancer (n=42,333)	Cervical cancer (n=19,282)
Age at diagnosis	64.4 (18–100)	67.0 (24–102)	51.4 (18–103)
Age			
18–49	4,721 (14)	2,109 (5)	10,346 (54)
50–74	20,232 (61)	28,858 (68)	6,394 (33)
>75	8,413 (25)	6,394 (33)	2,542 (13)
Period of diagnosis			
1989–1994	6,831 (20)	7,537 (18)	4,430 (23)
1995–2000	7,536 (23)	8,419 (20)	4,348 (23)
2001–2005	6,047 (18)	8,113 (19)	3,278 (17)
2006–2010	6,503 (19)	8,847 (21)	3,621 (19)
2011–2015	6,449 (19)	9,417 (22)	3,605 (19)
Vital status*	8,068 (24)	21,826 (52)	10,970 (57)
Previous gynecological tumor	1,119 (3)	1,080 (3)	226 (1)
Previous non-gynecological tumors	5,240 (16)	9,436 (22)	2,480 (13)
Socio-economic status			
High	10,296 (31)	12,548 (30)	5,651 (29)
Middle	13,663 (41)	17,344 (41)	6,987 (36)
Low	9,407 (28)	12,441 (29)	6,644 (35)
FIGO stage			
I	6,958 (21)	31,208 (74)	10,374 (54)
II	2,663 (8)	3,273 (8)	3,254 (17)
III	14,640 (44)	3,566 (8)	3,241 (17)
IV	5,809 (17)	2,389 (6)	1,857 (10)
Unknown	3,296 (10)	1,897 (5)	556 (3)
Differentiation grade			
I	3,249 (9)	16,607 (39)	1,134 (6)
II	5,527 (17)	13,331 (31)	5,391 (28)
III	11,996 (36)	7,601 (18)	4,961 (26)
Unknown	12,594 (38)	4,794 (11)	7,796 (31)
Histology			
Serous	13,603 (41)	1,493 (5)	-
Mucinous	3,378 (10)	-	-
Clear cell	1,520 (5)	824 (2)	-
Endometrioid	3,107 (9)	22,248 (53)	-
Squamous carcinoma	-	-	14,325 (74)
Adenocarcinoma NOS	9,243 (28)	13,574 (32)	3,410 (18)
Other	2,515 (8)	4,194 (10)	1,547 (8)
Peritoneal metastases	20,402 (61)	711 (2)	98 (1)

Values are presented as mean (range) or number (%).

*Vital status of all patients was assessed on February 1, 2017.

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Table 2. Patient and tumor characteristics of all patients with peritoneal metastases of ovarian, endometrial or cervical origin between 1989 and 2015 in the Netherlands (n=21,211)

Characteristics	Ovarian cancer (n=20,402)	Endometrial cancer (n=711)	Cervical cancer (n=98)
Age at diagnosis	65.7 (18–100)	69.1 (25–95)	61.5 (23–93)
Age			
18–49	2,181 (11)	28 (4)	23 (23)
50–74	12,885 (63)	462 (65)	50 (51)
>75	5,336 (26)	220 (31)	25 (26)
Period of diagnosis			
1989–1994	3,672 (18)	44 (6)	5 (5)
1995–2000	4,359 (21)	53 (7)	6 (6)
2001–2005	3,729 (18)	73 (10)	14 (14)
2006–2010	4,257 (21)	196 (28)	27 (28)
2011–2015	4,384 (21)	345 (49)	46 (47)
Previous gynecological tumor	350 (2)	17 (2)	1 (1)
Previous non-gynecological tumors	2,450 (12)	129 (18)	12 (12)
Socio-economic status			
High	6,276 (31)	194 (27)	17 (17)
Middle	8,444 (41)	315 (44)	43 (44)
Low	5,682 (28)	202 (28)	38 (39)
Metastatic pattern			
PM alone	18,083 (89)	554 (78)	54 (55)
PM + positive lymph nodes	531 (3)	53 (7)	18 (18)
PM + (other) distant metastases	1,620 (8)	93 (13)	16 (16)
PM + lymph nodes and distant metastases	168 (1)	9 (1)	10 (10)
FIGO stage			
I	1 (0)	2 (0.3)	0 (0)
II	29 (0.1)	0 (0)	0 (0)
III	13,960 (68)	2 (0.3)	1 (1)
IV	4,759 (23)	684 (96)	93 (95)
Unknown	1,653 (8)	23 (3)	4 (4)
Differentiation grade			
I	847 (4)	41 (6)	2 (2)
II	2,994 (15)	97 (14)	15 (15)
III	8,701 (43)	326 (46)	33 (34)
Unknown	7,860 (38)	247 (34)	48 (49)
Histology			
Serous	10,390 (51)	196 (28)	-
Mucinous	1,064 (5)	-	-
Clear cell	424 (2)	44 (6)	-
Endometrioid	989 (5)	221 (31)	-
Squamous carcinoma	-	-	43 (44)
Adenocarcinoma NOS	6,587 (32)	110 (15)	37 (38)
Other	948 (5)	140 (20)	18 (18)

Values are presented as mean (range) or number (%).

FIGO, International Federation of Gynecology and Obstetrics; NOS, not otherwise specified; PM, peritoneal metastases.

in registration from 2005 onwards showed a non-significant decrease in the age-adjusted incidence of PM ($p=0.33$). An age at diagnosis between 50 and 74 years was associated with an increased risk of PM (odds ratio [OR]=1.19; 95% confidence interval [CI]=1.08–1.32) compared to an age between 18 and 49 years (**Table 3**). A reduced risk was seen in patients with an age at diagnosis above 75 years (OR=0.85; 95% CI=0.76–0.95) and a medical history of one or more non-gynecological tumors (OR=0.65; 95% CI=0.60–0.71). Serous histology showed to have the highest risk of PM, compared to other histological subtypes. The risk of PM was higher in patients with a moderate to poor differentiation grade (grade II and III) compared to good differentiation grade (grade I) and with the presence of distant metastases (OR=1.25; 95% CI=1.10–1.41). The presence of positive lymph nodes reduced the risk of PM (OR=0.76; 95% CI=0.63–0.93).

Incidence and predictors of peritoneal metastases

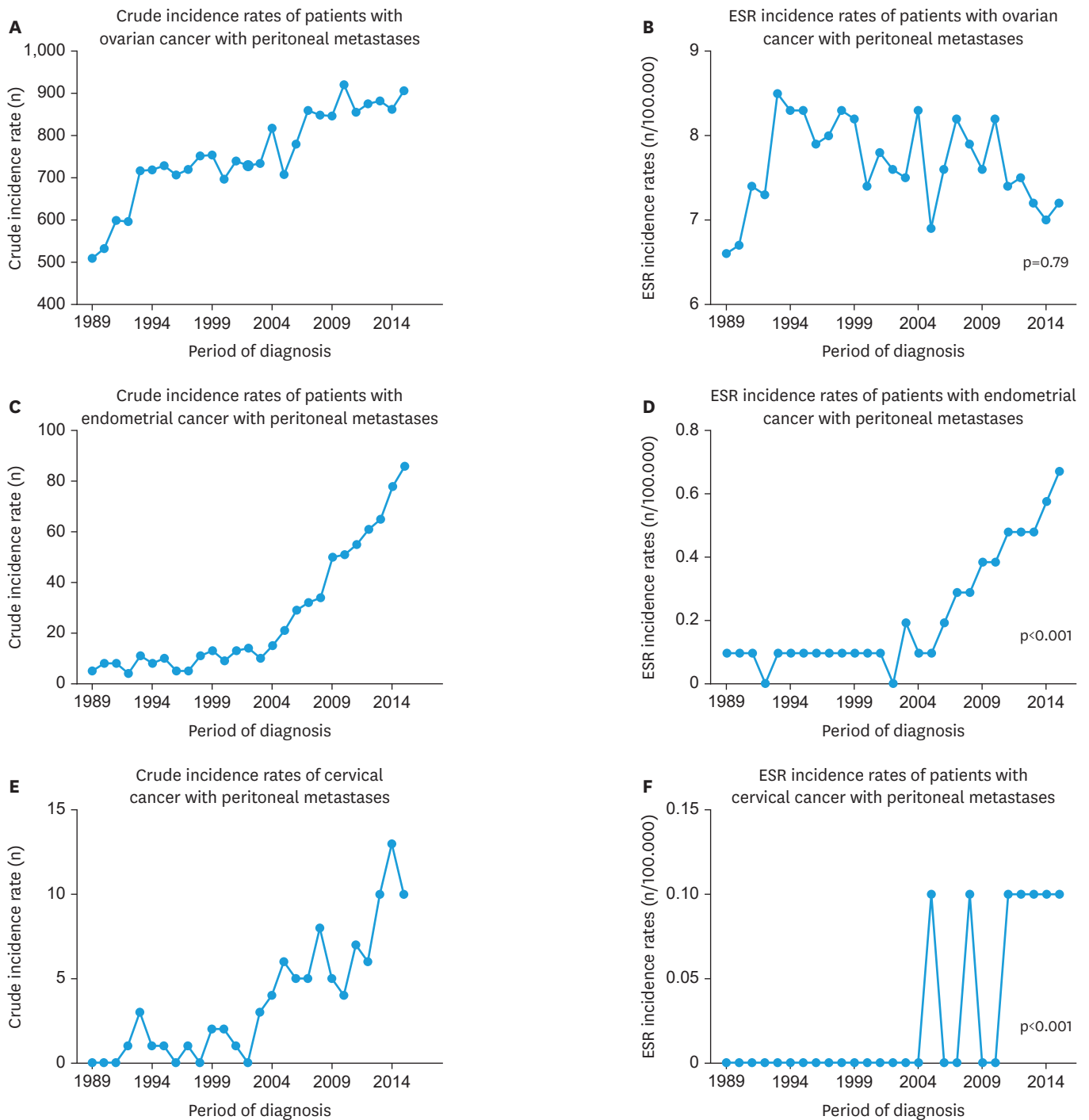


Fig. 2. Crude and European standardized incidence rates for peritoneal metastases in patients with ovarian (A, B), endometrial (C, D) and cervical cancer (E, F) between 1989 and 2015 in the Netherlands.

2. Endometrial cancer with PM

In all endometrial cancer patients, the vast majority was diagnosed in FIGO stage I disease (74%). Only 2% (n=709) presented with PM. The mean age at diagnosis for advanced stage patients was 69.1 years. The most common histological subtypes were endometrioid (31%) and serous (28%) and 78% had no other metastases than PM. An increase in crude and age-adjusted ($p < 0.001$)

Incidence and predictors of peritoneal metastases

Table 3. Multivariable logistic regression analyses: predictors of having peritoneal metastases in patients diagnosed with advanced stage gynecological cancer between 1995 and 2015 in the Netherlands

Characteristics	Ovarian cancer	Endometrial cancer	Cervical cancer
Age			
18–49	Ref.	-	-
50–74	1.19 (1.08–1.32)	-	-
>75	0.85 (0.76–0.95)	-	-
Socio-economic status			
High	Ref.	-	-
Middle	0.97 (0.90–1.05)	-	-
Low	0.91 (0.84–0.99)	-	-
More non-gyn tumors			
Yes	0.65 (0.60–0.71)	-	-
No	Ref.	-	-
Metastatic pattern			
No lymphatic or distant metastases	Ref.	Ref.	Ref.
Positive lymph nodes	0.76 (0.63–0.93)	2.32 (1.65–3.26)	4.16 (2.38–7.28)
Distant metastases	1.25 (1.10–1.41)	1.38 (1.08–1.77)	3.46 (1.90–6.30)
Lymph nodes and distant metastases	0.64 (0.48–0.88)	0.75 (0.37–1.51)	5.19 (2.53–10.66)
Differentiation grade			
I	Ref.	Ref.	Ref.
II	1.78 (1.51–2.08)	1.13 (0.77–1.65)	1.16 (0.26–5.19)
III	2.00 (1.73–2.32)	1.95 (1.38–2.76)	1.52 (0.35–6.51)
Unknown	1.70 (1.47–1.97)	2.56 (1.77–3.70)	2.24 (0.53–9.49)
Histology			
Adenocarcinoma NOS	0.54 (0.50–0.58)	0.61 (0.48–0.77)	4.92 (3.11–7.79)
Serous	Ref.	2.71 (2.15–3.42)	-
Mucinous	0.51 (0.44–0.58)	-	-
Clear cell	0.22 (0.18–0.26)	1.49 (1.04–2.13)	-
Endometrioid	0.25 (0.22–0.28)	Ref.	-
Squamous carcinoma	-	-	Ref.
Other	0.11 (0.10–0.12)	1.04 (0.81–1.34)	2.72 (1.46–5.05)

Values are presented as odds ratio (confidence interval). All odds ratios are adjusted for the listed variables.

incidence of PM was seen (**Fig. 2C and D**), as well as in a subgroup analysis of age-adjusted incidence rates between 2005 and 2015 ($p < 0.001$). The risk of PM was increased in serous (OR=2.71; 95% CI=2.15–3.42) and clear cell (OR=1.48; 95% CI=1.04–2.13) subtypes compared to the endometrioid subtype. A moderate to poor differentiation grade (grade II and III) increased the risk as well. Other distant metastases than PM (OR=1.38; 95% CI=1.08–1.77) and affected lymph nodes (OR=2.32; 95% CI=1.65–3.26) were associated with a higher risk on PM.

3. Cervical cancer with PM

One percent ($n=98$) of all cervical cancer patients presented with PM. The mean age at diagnosis of only advanced stage patients was 51.4 years. Thirty-eight percent had an adenocarcinoma and 44% had a squamous cell carcinoma. Fifty-five percent of patients had PM without other distant metastases. An increase in crude and age-adjusted ($p < 0.001$) incidence of PM is seen (**Fig. 2E and F**); a subgroup analysis of age-adjusted incidence rates between 2005 and 2015 did underline this increase ($p=0.019$). The risk of PM was higher in adenocarcinoma compared to squamous cell carcinoma (OR=4.92; 95% CI=3.11–7.79). For cervical cancer, every type of metastatic pattern was significantly associated with the occurrence of PM.

DISCUSSION

This study showed that PM are most common in ovarian cancer when studying gynecological cancers. Moreover, more than half of all ovarian cancer patients presented with PM,

negatively influencing overall survival rates. In addition to serous ovarian cancer patients, serous and clear cell endometrial cancer patients and patients with adenocarcinoma of the cervix are at highest risk for the occurrence of PM.

Although the majority of PM were found in ovarian cancer patients, our data show that PM also occur in endometrial and cervical cancer. In case of endometrial cancer this is in line with 2 previous review articles [16,17].

The age-adjusted incidence of PM in ovarian cancer was stable between 1989 and 2015. In endometrial cancer a significant increase in incidence was observed and might be explained by the increase of surgical staging in high-risk endometrial cancer over time, ever since national guidelines recommend to conduct a surgical exploration and extensive staging in case of serous and clear cell endometrial cancer [18]. This, together with the improvement of radiological diagnostics such as computed tomography-scans, can explain the significant increase in the incidence of PM of endometrial cancer. In cervical cancer, incidence rates are based on a small number of patients.

As stated previously, our results show that histological subtype is the strongest predictor for the occurrence of PM. For example, PM occur more often in serous ovarian and endometrial cancers and in adenocarcinomas of the cervix than in squamous cell carcinomas, which is in line with a previous study [19]. In addition, a moderate to poor differentiation grade is an independent predictor for the occurrence of PM in ovarian and endometrial cancer. Previous studies in colorectal and gastric cancer patients show similar predictive factors like histological type and differentiation grade [20,21]. In those studies, PM were also more often found in younger patients (below 60 years), which is in line with our findings in ovarian cancer patients. Probably this is due to the fact that older patients less often underwent surgical exploration of the peritoneal cavity. This effect was eliminated as much as possible by extracting data on PM from surgical, pathological and radiological reports. A small percentage of the, mainly older, patients will still not have gone through a full diagnostic workup and some data may be lacking [22]. Our data also suggest that the risk of PM in ovarian cancer is reduced in case of a previous non-gynecological cancer. We cannot explain this in a biological way but we suspect that these patients (and cancer patients in generally) are more often exposed to thorough examinations, leading to diagnosis in an earlier stage.

In ovarian cancer patients with affected lymph nodes, a lower risk of PM was found. This is consistent with the revised FIGO staging system, in which the presence of affected lymph nodes is now considered to be FIGO stage IIIa disease instead of FIGO stage IIIc disease [23]. However, in endometrial and cervical cancer patients the risk of PM was significantly increased in case of affected lymph nodes. This pattern was seen in colorectal and gastric cancer as well [20,21]. This difference may well be explained by the biological behavior of ovarian cancer versus endometrial and cervical cancer. In ovarian cancer, an increasing amount of evidence for the 'tubal-hypothesis' exists, which suggests that ovarian cancer originates in the epithelium of the fallopian tube and spread throughout the abdomen [24]. In endometrial and cervical cancer, like in colorectal cancer, PM are caused by serosal infiltration of the primary tumor and subsequent shedding of malignant cells into the peritoneal cavity [25]. One can imagine that this difference in biological behavior and aggressiveness can also influence the occurrence of affected lymph nodes.

A lack of lymph node sampling in ovarian cancer patients may play a role as well. In patients with gross intra-abdominal disease, and macroscopically normal lymph nodes, standard

lymphadenectomy does not contribute to prolonged overall nor progression-free survival in these patients [26,27]. This might influence the correlation between affected lymph nodes and the risk on PM. It also may be a consequence of the retrospective design of our study.

This study adds to the literature on the biological behavior of gynecological tumors and this may contribute to the development of more effective therapeutic strategies. As our study and other population-based studies pointed out, the peritoneum is a preferred localization for metastases of various kinds of cancer [3,20,21]. Therefore, the most important clinical consequence of identifying predictors for the occurrence of PM is the development of a more targeted treatment strategy, like intraperitoneal (IP) chemotherapy. Upcoming treatment strategies like hyperthermic intraperitoneal chemotherapy (HIPEC) are promising. In IP chemotherapy and HIPEC, the drugs are administered directly into the peritoneal cavity, increasing the drug's dose delivered to the tumor site [28-30]. Several studies show the beneficial effect of IP chemotherapy after cytoreductive surgery for ovarian cancer patients, resulting in an increase of median survival [31-34]. Other studies, including a recent Dutch study, demonstrated the beneficial effect of HIPEC on recurrence free and overall survival in ovarian cancer patients [35-39]. In our study, we have shown that serous and clear cell histology in endometrial cancer is an independent predictor for the occurrence of PM. Therefore, treatment strategies used for ovarian cancer could be considered for these types of cancers as well, i.e., extensive cytoreductive surgery in combination with chemotherapy. The indication for IP chemotherapy or even HIPEC in serous and clear cell endometrial cancer could be subject for future studies, taking into account the quality of life after such treatment strategies [40-42].

Our study provides an overview of population-based data over more than twenty-five years. The retrospective design however has its limitations. One is the extraction of data from medical files; some details on background information were missing. Also, because PM are best diagnosed during an operative procedure, one might speculate that this study could underestimate the true incidence of PM. This might specifically be the case in older patients or in patients who for other reasons did not undergo a surgical procedure. There might be some bias because of increasing adequacy of pathological methods influencing the diagnosed histological type of a cancer, especially in case of adenocarcinoma NOS subtypes.

In conclusion, PM are frequently seen in patients with ovarian cancer. Ovarian cancers, serous and clear cell endometrial cancers and adenocarcinoma of the cervix have the highest risk for the occurrence of PM. Therefore, we suggest a therapeutic approach in which a cancer is treated in accordance with its histological subtype and its pattern of metastasis. Considering the possible beneficial effect of IP chemotherapy and HIPEC on the survival of advanced stage ovarian cancer patients, this might be a starting point for new research into those treatment strategies in patients with serous or clear cell endometrial cancer and adenocarcinoma of the cervix.

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