Received: 21 December 2025 | Revised: 4 March 2026 | Accepted: 9 March 2026

DOI: 10.1111/aogs.70202

ORIGINAL RESEARCH

Subsequent pregnancies after a diagnosis of pregnancy-associated cancer

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Funding information
European Union-Next Generation EU

Abstract

Introduction: Pregnancy-associated cancer is a rare but clinically significant event. Decisions regarding subsequent pregnancies after such a diagnosis are complex and influenced by medical, psychological, and social factors. This study aimed to investigate the probability of having a subsequent pregnancy following a diagnosis of a pregnancy-associated cancer.

Material and Methods: We conducted a record-linkage cohort study using the regional health databases of Lombardy, including the hospital discharge records and the certificate of delivery assistance. Pregnancies were deliveries and abortions occurring between 1 January 2007 and 31 December 2017. Pregnancy-associated cancer was defined as any malignant neoplasm first diagnosed during pregnancy or within 1 year after the end of pregnancy, identified through hospital admissions carrying a new cancer diagnosis. To ascertain subsequent pregnancies after a diagnosis of pregnancy-associated cancer, we tracked deliveries and abortions through 31 December 2023. We estimated the incidence of pregnancy-associated cancer per 1000 pregnancies with the corresponding 95% confidence intervals (CIs) and calculated the cumulative probability of a post-diagnosis pregnancy using the cumulative incidence function that accounts for the competing risk of death.

Results: A total of 832 incident pregnancy-associated cancers were recorded among deliveries and 325 among abortions, corresponding to incidence rates of 1.12 per 1000 deliveries (95% CI, 1.04–1.19) and 1.27 per 1000 abortions (95% CI, 1.13–1.41). Breast cancer was the most frequent diagnosis in both groups (31% among deliveries, 40% among abortions), followed by thyroid cancer; the third most common site was lymphoma among deliveries and cervical cancer among abortions. During follow-up, 77 women had a subsequent pregnancy (59 deliveries, 18 abortions), yielding a cumulative probability of 7.3%. Stratified by age at diagnosis, women under 35 had a substantially higher probability of subsequent pregnancy compared to women aged 35 or older (14.0% vs. 3.5%, $p < 0.01$). Furthermore, the

cumulative probability of subsequent pregnancy was lower among women treated with antineoplastic therapy than among those who were not treated (4.3% vs. 10.1%, $p < 0.01$).

Conclusions: Subsequent pregnancies following a pregnancy-associated cancer diagnosis were relatively uncommon, highlighting the need for integrated reproductive counseling within a multidisciplinary approach.

KEYWORDS

fertility counseling, maternal health, pregnancy-associated cancer, reproductive outcomes, subsequent pregnancy

1 | INTRODUCTION

Pregnancy-associated cancer—a malignancy diagnosed during pregnancy or within 12 months postpartum—is a rare but clinically relevant event, affecting approximately 1 in 1000–2000 pregnancies.[1] A rise in pregnancy-associated cancers is expected in the near future due to advanced maternal age, increased obesity, greater awareness of the importance of screening and self-examination, and improved diagnostic techniques.[2]

Although there is substantial evidence about the negative psychological impact of cancer, few studies examined the subjective experience of women with pregnancy-associated cancer,[3] who may not have yet reached their desired family size. Improvements in cancer treatment and obstetric care have increased survival rates, prompting more women to consider having children even after a diagnosis of pregnancy-associated cancer. This adds an additional layer of complexity to their emotional and clinical management.

The decision to pursue a subsequent pregnancy after a diagnosis of pregnancy-associated cancer is complex and influenced by medical, psychological, and social factors. Concerns are often centered on the potential impact of a subsequent pregnancy on prognosis, on prior cancer treatments on fertility, and on long-term maternal health. In addition, questions remain regarding possible risks to the fetus and the timing of conception in relation to cancer remission.

Evidence on reproductive opportunities after pregnancy-associated cancer is scarce. Most studies on fertility and pregnancy after cancer exclude those diagnosed in the peripartum period,[4–7] for potential differences in cancer biology, treatment timing, and maternal physiology. Thus, the impact of prior pregnancy-associated cancer on the likelihood of subsequent pregnancy, pregnancy outcomes, and long-term maternal survival remains poorly characterized.

This record-linkage study investigates the incidence, timing, and outcomes of pregnancies after a pregnancy-associated cancer diagnosis. Our findings aim to address this gap by informing clinical counseling, guiding reproductive planning, and supporting survivorship care strategies to optimize both maternal and child health.

Key message

Subsequent pregnancies after a pregnancy-associated cancer diagnosis are possible. These findings highlight the importance of integrating reproductive counseling into routine care, especially for younger patients, and underscore the need for collaborative management among oncologists, obstetricians, and fertility specialists.

2 | MATERIAL AND METHODS

2.1 | Study design and data sources

Italy has a publicly funded, universal National Health Service which provides free or subsidized healthcare to all residents. However, healthcare delivery and data collection are organized at the regional level. We conducted a record-linkage cohort study using linked regional health databases from Lombardy, Italy (approximately 10 million inhabitants).

For the present study, data sources included hospital discharge records (Scheda di Dimissione Ospedaliera, SDO) from public and private hospitals and the Certificate of Delivery Assistance (Certificato di Assistenza al Parto, CedAP), a standardized birth record containing maternal demographics, obstetric history, and delivery details.

Individual-level records were deterministically linked via a unique personal identifier; all identifiers were anonymized before analysis. This linkage enabled the construction of large, population-based birth cohorts and the generation of real-world evidence on maternal and perinatal outcomes.

2.2 | Study population

We identified all deliveries and abortions that occurred in the region between 1 January 2007 and 31 December 2017. Deliveries were identified through the CedAP forms and the corresponding hospital admission for childbirth, while abortions were identified using the SDO forms (diagnosis ICD-9-CM codes: 632.xx-639.xx, V132; intervention ICD-9-CM codes: 69.0x, 69.5x, 74.91, 75.0x; DRG codes: 380–381). We sequentially excluded: (i) deliveries or abortions of women not covered by the National Health Service during the 3 years prior to conception or the abortion admission date, and the year following delivery or the abortion admission date, (ii) deliveries or abortions involving women younger than 15 or older than 55 years, (iii) deliveries occurring before 22 + 0 or after 42 + 6 weeks of gestation, and (iv) deliveries without a corresponding neonatal form.

Among these, we identified cases of pregnancy-associated cancer, defined as any cancer diagnosed during pregnancy, from conception to the date of delivery or admission for abortion, or within 1 year of the end of pregnancy. This included any hospital admission with ICD-9-CM cancer diagnostic codes 140–208, whether recorded as a principal or secondary diagnosis. The date of conception was based on the delivery date and gestational age. In the case of abortion, it was conventionally estimated as 3 months prior to the admission date. To ensure the inclusion of only newly diagnosed cases, we excluded prevalent cases, defined as women with a history of cancer, identified by at least one cancer-related hospital discharge prior to conception. When a woman had more than one pregnancy-associated cancer, only the first event was considered.

Antineoplastic treatment was defined as the presence of at least one of the following: a hospital discharge diagnosis or procedure relating to antineoplastic therapy; an outpatient visit indicating antineoplastic treatment; or an inpatient drug prescription for an antineoplastic drug (ATC code: L01, which includes alkylating agents, antimetabolites, plant alkaloids and other natural products, cytotoxic antibiotics and related substances, protein kinase inhibitors, monoclonal antibodies and antibody-drug conjugates, and other antineoplastic agents). A woman was considered to have received treatment if she was administered antineoplastic therapy from 1 year before the hospital admission used to define the cancer diagnosis until 1 year after. Including the year before hospitalization was intended to minimize misclassification of treatment exposure in cases where the initial cancer diagnosis occurred in an outpatient setting and preceded the first cancer-related hospital admission. The selection process took place in July 2025.

2.3 | Outcome: Subsequent pregnancy following a pregnancy-associated cancer diagnosis

To determine whether a pregnancy occurred after the pregnancy-associated cancer diagnosis, which is defined as the date of hospital admission for cancer, we considered all deliveries recorded in the CedAP database between 1 January 2007 and 31 December 2023 and all abortions recorded in the hospital discharge database in the same period.

2.4 | Data analysis

We calculated the incidence rate of pregnancy-associated cancer per 1000 pregnancies and the corresponding 95% confidence interval (CI) as the number of pregnancy-associated cancer cases divided by the total number of pregnancies. The rates in strata of pregnancy outcome (i.e., delivery or abortion) were also computed.

The cumulative probability of pregnancy among women diagnosed with pregnancy-associated cancer was estimated using the cumulative incidence function to account for the competing risk of death according to the Kalbfleisch–Prentice method. This was repeated in strata of pregnancy outcome, maternal age, and antineoplastic treatment. Each woman accumulated person-years of follow-up from delivery or abortion date until the earliest of the following: subsequent delivery or admission for subsequent abortion date, exit from regional healthcare coverage, death, 31 December of the year in which she turned 55, or 31 December 2023. Women were censored if they moved out of the region or did not have a delivery by the end of follow-up. Gray's test was used to compare cumulative incidence curves in stratified analyses.

All analyses were performed using the Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC, USA).

Data were handled anonymously. Ethical approval was not required in Italy for this study.

3 | RESULTS

Between 1 January 2007 and 31 December 2017, we identified 745 932 deliveries and 255 364 abortions. A total of 832 and 325 incident cases of pregnancy-associated cancer were recorded in each group, respectively. This corresponds to a pregnancy-associated cancer incidence rate of 1.12 per 1000 deliveries (95% CI: 1.04–1.19) and 1.27 per 1000 abortions (95% CI: 1.13–1.41). The detailed cohort selection process is illustrated in the flow chart shown in Figure 1.

Table 1 presents the distribution of maternal age, parity (available only for deliveries), and cancer site, stratified by pregnancy outcome. Among women with pregnancy-associated cancer, most cases associated with pregnancies ending in delivery occurred in women aged ≥35 years (58.3%). In the group associated with pregnancies ending in abortions, an even higher proportion (76.9%) were aged ≥35 years. As for parity, 57.1% of pregnancy-associated cancer occurred in parous women. In terms of cancer site, breast cancer was the most frequent pregnancy-associated cancer in both groups, accounting for 31.0% of cases that ended in delivery and 40.0% ended in abortion. The second most common cancer site in both groups was thyroid, representing 15.0% of cases after deliveries and 12.6% after

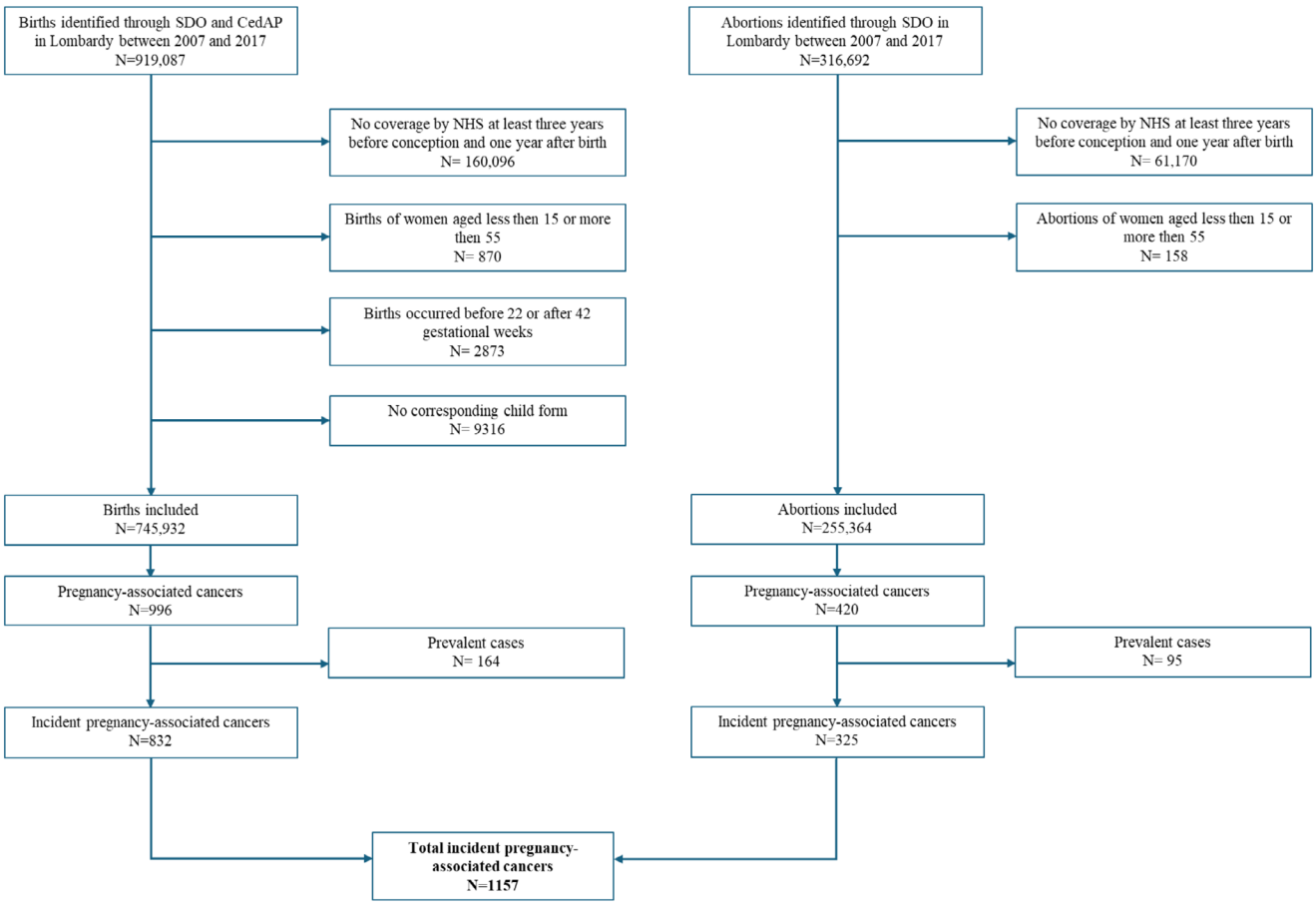

FIGURE 1 Flowchart of cohort selection. CedAP, certificate of delivery assistance; NHS, National Health Service; SDO, Scheda di Dimissione Ospedaliera (hospital discharge form).

abortions. The third most common cancer site varied by pregnancy outcome: lymphoma accounted for 9.1% of pregnancy-associated cancers ended in deliveries, whereas cervical cancer accounted for 6.2% of pregnancy-associated cancers ended in abortions.

Overall, 522 women (45.1%) underwent antineoplastic therapy. Treatment was administered to 58.9% of women with breast cancer, none of those with thyroid cancer, and 75.3% of those with lymphoma.

In total, 59 women who had previously been diagnosed with pregnancy-associated cancer had a delivery, and 18 had an abortion (4 were spontaneous, 13 were induced, and one unspecified), giving respective cumulative probabilities of 5.6% and 2.0%. Three experienced both a delivery and an abortion, 2 had a spontaneous abortion first and then a delivery, and one had a delivery and then a spontaneous abortion. Figure 2 shows that the cumulative probability of subsequent pregnancy for women diagnosed with pregnancy-associated cancer was 7.3%.

Overall, women diagnosed with pregnancy-associated cancer who had an abortion had a higher cumulative probability of subsequent pregnancy (9.0%) compared to those whose pregnancy ended in a delivery (6.7%). However, this difference was not significant ($p = 0.25$). When stratified by maternal age at pregnancy-associated cancer diagnosis, the cumulative probability of subsequent pregnancy was substantially higher among women aged less than 35 (14.0%) compared to those aged 35 or over (3.5%, $p < 0.01$). Women who received antineoplastic therapy experienced a reduced cumulative probability of subsequent pregnancy (4.0%) compared to those who did not receive such treatment (10.1%, $p < 0.01$).

4 | DISCUSSION

In this record-linkage cohort study from Lombardy, we found that subsequent pregnancies following a pregnancy-associated cancer diagnosis were relatively uncommon, with an overall cumulative probability of 7.3% during follow-up. Women diagnosed before the age of 35 were more likely to have a subsequent pregnancy than women aged 35 or over (14.0% vs. 3.5%). Furthermore, women who underwent antineoplastic treatment were less likely to experience a subsequent pregnancy than those who did not receive treatment (4.0% vs. 10.1%). Breast cancer was the most frequent pregnancy-associated cancer in both deliveries and abortions, followed by thyroid cancer and lymphomas. This is consistent with previous reports on the distribution of pregnancy-associated cancer sites.[8,9]

TABLE 1 Maternal characteristics and distribution of cancer sites in pregnancy-associated cancer cases according to outcome.

	Pregnancy-associated cancers			
	Ended in deliveries		Ended in abortions	
	n = 832	(%)	*n = 325*	(%)
Maternal age				
<35	347	(41.7)	75	(23.1)
≥35	485	(58.3)	250	(76.9)
Parity				
0	357	(42.9)	—	—
≥1	475	(57.1)	—	—
Cancer site				
Breast	258	(31.0)	130	(40.0)
Thyroid	125	(15.0)	41	(12.6)
Lymphoma	76	(9.1)	17	(5.2)
Cervix	54	(6.5)	21	(6.5)
Skin	49	(5.9)	7	(2.2)
Colon-rectum	27	(3.2)	16	(4.9)
Nervous system	27	(3.2)	10	(3.1)
Ovary	21	(2.5)	4	(1.2)
Melanoma	20	(2.4)	4	(1.2)
Skeleton	19	(2.3)	5	(1.6)
Leukemia	18	(2.2)	4	(1.2)
Placenta	5	(0.6)	17	(5.2)
Kidney	18	(2.2)	2	(0.6)
Head and neck	15	(1.8)	2	(0.6)
Urinary tract	10	(1.2)	3	(0.9)
Lung	8	(1.0)	3	(0.9)
Stomach	4	(0.5)	5	(1.5)
Pancreas	4	(0.5)	4	(1.2)
Endometrium	1	(0.1)	2	(0.6)
Liver	2	(0.2)	1	(0.3)
Metastases	46	(5.5)	22	(6.8)
Other sites	23	(2.8)	5	(1.5)
Not defined	2	(0.2)	0	(0.0)

Women diagnosed with pregnancy-associated cancer are exposed to multiple sources of stress. Pregnancy itself is a moment of major life transition, with remarkable psychological and physical changes that can be emotionally challenging for any woman.[3] The co-occurrence of pregnancy and cancer represents a unique condition associated with short- and long-term negative psychological outcomes.[10] Recently, Facchin et al.[11] conducted a qualitative study to provide an in-depth exploration of women's experiences of being diagnosed with breast cancer during pregnancy. The study focused particularly on their emotional responses, concerns, challenges, available resources, and post-diagnosis needs. A key theme that emerged was the sense of difference and the comparison with healthy women. Simultaneously experiencing cancer and pregnancy can generate profound psychological distress, arising from both the physical and emotional effects of oncological treatments and a strong desire to experience a "normal" pregnancy.

Our findings are consistent with previous evidence suggesting that, while relatively rare, pregnancy after a pregnancy-associated cancer—particularly breast cancer—is feasible for some survivors.[12,13] However, most prior studies have focused on cancers diagnosed outside pregnancy or in the subsequent year after delivery, where the biological characteristics of the tumor and the course of treatment may differ.[4–7] In the event of pregnancy-associated cancer, treatment decisions include those made in the context of an ongoing or recent pregnancy.[14] This can result in changes in the timing and type of therapy, potentially affecting fertility preservation and subsequent reproductive potential.

We observed that women whose pregnancy-associated cancer was associated with an abortion had a slightly higher cumulative probability of a subsequent pregnancy than ones associated with a delivery (8.8% vs. 6.6%), although the difference was not significant. This may depend on parity, cancer stage, or the aggressiveness of treatment, factors which are not fully captured from our data.

The strong inverse association between maternal age at pregnancy-associated cancer diagnosis and probability of subsequent pregnancy is consistent with established age-related declines in fertility, which may be further increased by gonadotoxic treatments. Younger women are also more likely to receive counseling about fertility preservation and to have greater reproductive intent post-treatment. In addition to the decline in biological fertility that occurs with age, psychosocial and contextual factors may also influence reproductive decision-making. For example, younger women may have a stronger desire to have children or feel a greater sense of urgency to complete their families, whereas older women may already have achieved their desired family size by the time they are diagnosed. The recommended delay in conception following treatment may disproportionately affect older women, who have a shorter remaining reproductive window. Taken together, these findings suggest that both biological constraints and age-specific psychosocial factors likely contribute to the observed differences in post-cancer reproductive behavior. Integrating individualized fertility counseling and psychosocial assessment into survivorship care may help address modifiable barriers and support informed reproductive planning over time.

Although subsequent pregnancy is possible after a pregnancy-associated cancer, it remains uncommon. This low probability is likely due to a combination of biological, medical, and psychosocial barriers. Women may delay or avoid pregnancy due to fears of cancer recurrence or concerns about the safety of pregnancy after treatment. This is particularly likely if counseling is inconsistent or overly cautious. Socioeconomic factors, such as employment stability and access to fertility counseling or assisted reproductive technologies, can also affect the likelihood and timing of subsequent pregnancies.

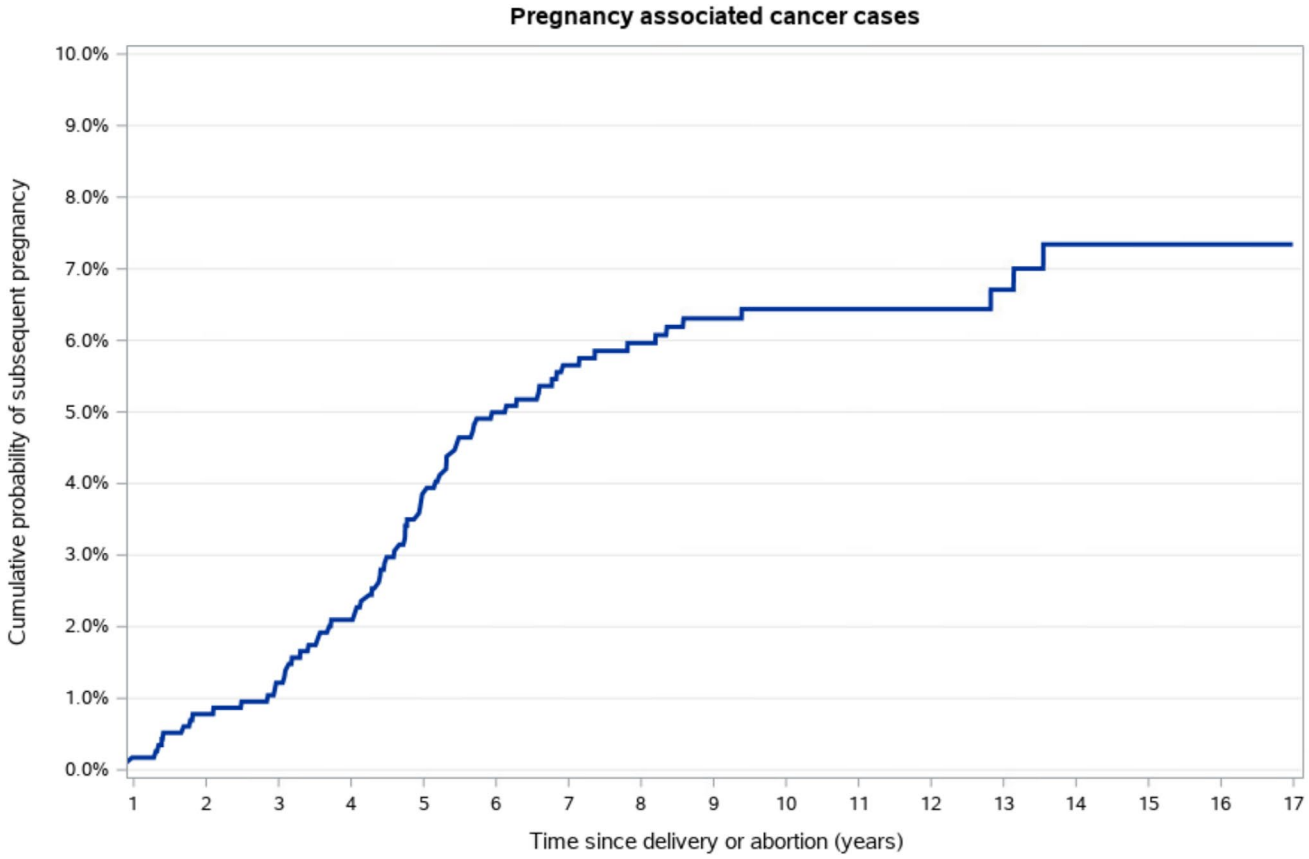

FIGURE 2 Cumulative probability of a subsequent pregnancy after a diagnosis of pregnancy-associated cancer.

Furthermore, partnership status and the presence or absence of social support can affect both the intention to have children and the feasibility of doing so after cancer. Notably, our data also indicate that subsequent pregnancies can occur several years after pregnancy-associated cancer diagnosis, underscoring the importance of long-term reproductive follow-up in survivorship care plans.

The strengths of our study include its population-based design, comprehensive coverage of both public and private healthcare facilities, and deterministic record linkage across regionally based databases, which minimizes selection bias and loss to follow-up.

Among the possible limitations, we did not use dedicated cancer registry data to define diagnoses; instead, our definition of a cancer diagnosis was based on hospital admission for malignant disease. Therefore, if the initial diagnosis occurred in an outpatient setting, hospital discharge data may not accurately capture the exact date of cancer onset. Furthermore, cancers that were managed exclusively in outpatient settings and did not require hospitalization may not have been captured, which could lead to underascertainment to some degree. However, findings from Italian studies,[15,16] which linked population-based cancer registries with hospital discharge records, support the use of hospital data to estimate the incidence of pregnancy-associated cancers. In these studies, up to 21 regional cancer registries, covering around 30% of the Italian population, were individually linked with hospital discharge records. This yielded an estimated rate of pregnancy-associated cancers of approximately 1.24–1.43 per 1000 pregnancies, similar to our own estimates based solely on hospital data.

We also lacked core clinical information on cancer stage, histology, treatment modality (e.g., chemotherapy, radiotherapy, endocrine therapy), and time to remission. These factors are strongly associated with ovarian reserve and gonadotoxicity risk, fertility preservation counseling, the feasibility and timing of subsequent conception, and prognosis and survival. Their absence limits our ability to fully contextualize differences in subsequent pregnancy probabilities across subgroups and limits causal interpretation due to potential residual confounding by disease severity and treatment intensity. In particular, our results may reflect a selection of healthier cancer survivors—those with less aggressive disease or lower treatment intensity—who are more likely to survive, complete therapy, and pursue pregnancy. Conversely, the impact of more gonadotoxic treatments on reproductive outcomes may be underestimated. Although administrative data does not provide detailed clinical information, we incorporated available indicators of disease severity and treatment exposure (i.e., antineoplastic treatment). While these measures do not fully capture clinical complexity, they partially mitigate the effects of residual confounding factors such as disease severity and treatment intensity. Nevertheless, some degree of unmeasured confounding may persist.

Further, administrative data does not capture early miscarriages unless hospitalization occurs. Given that early pregnancy losses that

do not require hospitalization, especially in recent years, are relatively frequent, this omission may result in a non-negligible underestimation of the total number of pregnancy attempts after a diagnosis of pregnancy-associated cancer.

In addition, we were unable to assess recurrence risk directly, and our findings should not be interpreted as evidence of oncologic safety without complementary clinical data. As we did not have information on cancer recurrence, disease-free survival or overall survival, our findings cannot be interpreted as evidence regarding the safety of pregnancy after PAC. Instead, our results describe the incidence and timing of subsequent pregnancies among survivors in routine clinical practice.

Finally, while the study setting benefits from universal healthcare access, the generalizability of the findings to countries with different health systems may be limited.

These findings highlight the importance of integrating reproductive counseling into the care pathway for women with pregnancy-associated cancer, particularly younger patients, and underscore the need for collaborative care between oncologists, obstetricians, and fertility specialists to support informed reproductive decision-making after cancer.

5 | CONCLUSION

In this regional population-based cohort, approximately 1 in 15 women diagnosed with pregnancy-associated cancer went on to have a subsequent pregnancy, with markedly higher probabilities in those diagnosed before the age of 35 and those who did not undergo antineoplastic treatments.

AUTHOR CONTRIBUTIONS

Giovanna Esposito: Conceptualization, methodology, formal analysis, writing-original draft preparation; Fedro Alessandro Peccatori: Conceptualization, writing-review and editing; Matteo Franchi: Methodology, formal analysis, writing-review and editing; Giuseppe Trojano: Writing-review and editing; Giovanni Corrao: Writing-review and editing, supervision; Carlo La Vecchia: Writing-review and editing, supervision; Fabio Parazzini: Conceptualization, writing-original draft preparation, supervision; Anna Cantarutti: Methodology, formal analysis, writing-review and editing, supervision. All authors have read and approved the final version of the manuscript.

ACKNOWLEDGMENTS

Open access publishing facilitated by Universita degli Studi di Milano, as part of the Wiley - CRUI-CARE agreement.

FUNDING INFORMATION

This work is supported by the European Union-Next Generation EU, Mission 4, Component 1, CUP: H53D23006310001 (PRIN 2022. Real-world evaluation of cancer outcomes by integrating administrative and hospital-based health-related data: the “We-Care” project).

CONFLICT OF INTEREST STATEMENT

Among authors, Prof Giovanni Corrao received research support from the European Community (EC), the Italian Agency of Drugs (AIFA), and the Italian Ministry for University and Research (MIUR). He took part in a variety of projects that were funded by pharmaceutical companies (i.e., Novartis, GSK, Roche, AMGEN and BMS). He also received honoraria as a member of the advisory board to Roche. The other authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

Data that support the findings of this study are available from the Lombardy Region and are subject to legal restrictions under Italian data protection laws. Anonymized datasets analyzed during the current study can be provided on reasonable request from the authors, only after approval by the Lombardy Region.

ETHICS STATEMENT

Data used in this study were anonymized before their use. According to Italian law, studies based entirely on registry data are exempt from IRB authorization and informed consent.

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How to cite this article: Esposito G, Peccatori FA, Franchi M, et al. Subsequent pregnancies after a diagnosis of pregnancy-associated cancer. *Acta Obstet Gynecol Scand*. 2026;105:1096-1103. doi:10.1111/aogs.70202