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ORIGINAL RESEARCH

Increased Cancer Prevalence in Peripartum Cardiomyopathy

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ABSTRACT

OBJECTIVES This study was designed to analyze the prevalence and potential genetic basis of cancer and heart failure in peripartum cardiomyopathy (PPCM).

BACKGROUND PPCM manifests as heart failure late in pregnancy or postpartum in women without previous heart disease.

METHODS Clinical history and cancer prevalence were evaluated in a cohort of 236 PPCM patients from Germany and Sweden. Exome sequencing assessed variants in 133 genes associated with cancer predisposition syndromes (CPS) and in 115 genes associated with dilated/hypertrophic cardiomyopathy (DCM/HCM) in 14 PPCM patients with a history of cancer, and in 6 PPCM patients without a history of cancer.

RESULTS The prevalence of cancer was 16-fold higher (8.9%, 21 of 236 patients) in PPCM patients compared to age-matched women (German cancer registry, Robert-Koch-Institute: 0.59%; $p < 0.001$). Cancer before PPCM occurred in 12 of 21 patients of whom 11 obtained cardiotoxic cancer therapies. Of those, 17% fully recovered cardiac function by 7 ± 2 months of follow-up compared to 55% of PPCM patients without cancer ($p = 0.015$). Cancer occurred after PPCM in 10 of 21 patients; 80% had left ventricular ejection fraction of ≥50% after cancer therapy. Whole-exome sequencing in 14 PPCM patients with cancer revealed that 43% (6 of 14 patients) carried likely pathogenic (Class IV) or pathogenic (Class V) gene variants associated with DCM/HCM in CPT2, DSP, MYH7, TTN, and/or with CPS in ATM, ERCC5, NBN, RECQL4, and SLX4. All CPS variants affected DNA damage response genes.

CONCLUSIONS Cardiotoxic cancer therapy before PPCM is associated with delayed full recovery. The high cancer prevalence in PPCM is linked to likely pathogenic/pathogenic gene variants associated with DCM/HCM and/or CPS/DNA damage response–related cancer risk. This may warrant genetic testing and screening for heart failure in pregnant women with a cancer history and screening for cancer in PPCM patients. (J Am Coll Cardiol CardioOnc 2019;1:196–205)

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Peripartum cardiomyopathy (PPCM) is a life-threatening heart disease which emerges in the last month of pregnancy or in the first months after delivery in previously heart-healthy women. PPCM is defined as an idiopathic cardiomyopathy with left ventricular ejection fraction (LVEF) <45% with no other cause for heart failure found (1,2). The mechanisms leading to PPCM remain incompletely understood. A set of risk factors including pregnancy-associated hypertensive disorders, multiparity, higher maternal age, smoking, malnutrition, and infection are considered to play crucial roles (1,3).

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Previous work has examined links between the cardiotoxicity of cancer treatment and heart failure surrounding pregnancy and found that women who experienced cardiotoxicity had a higher risk for developing heart failure in pregnancy, whereas the risk is less substantial for women who do not experience short-term cardiotoxicity (4). However, registry data and case studies also suggest an association between cardiotoxic cancer therapies and PPCM even in patients who do not display left ventricular (LV) dysfunction immediately after cancer treatment (5,6). Recent data also suggest that heart failure may promote tumor growth, providing additional mechanistic evidence for an overlap between these 2 disease states (7). Thus, we hypothesized that there are important potential interactions between cancer disease and pregnancy-associated heart failure, particularly in PPCM, where the disease-inducing and pathophysiologic basis remain largely unknown (1,8–11). In the present study, we analyzed data from 236 PPCM patients from a German and a Swedish PPCM cohort to determine the incidence of cancer and changes in cardiac function over time. We performed exome sequencing in 133 genes associated with cancer predisposition syndromes (CPSs) and 115 genes associated with dilated/hypertrophic cardiomyopathy (DCM/HCM) in 20 participants from this well-phenotyped cohort.

METHODS

STUDY POPULATION. This study included 211 patients from the German PPCM registry (6) and 25 patients from a Swedish cohort for whom full medical history was available at the time of PPCM diagnosis. All 236 patients were enrolled into the registries between 2004 and 2018. Both studies were approved by the respective local ethics committees and all patients provided appropriate written informed consent. All patients met the diagnostic criteria of PPCM including the absence of documented previous heart disease and LVEF <45% (2).

Detailed information regarding their PPCM diagnosis was provided by all patients, either by medical records or by phone interview. Detailed clinical history, such as onset of symptoms and signs during first presentation, New York Heart Association functional class, electrocardiogram (ECG), echocardiograms, family history, diseases during pregnancy, and the mode of delivery were obtained from the patients, the referring physician, and by examining the obstetric and medical records. Furthermore, patients were divided into subgroups depending on their cardiac status at 7 ± 2 months of follow-up: no recovery (LVEF ≤35%; heart transplant [HTX]; left ventricular assist device [LV assist device implantation or death); partial recovery (LVEF >35% to 49%); and full recovery (LVEF ≥50%).

In 207 patients, information regarding the occurrence of cancer was also provided. Cancer prevalence in the cohort was compared to the 10-year prevalence in age-matched women (from 0 to 49 years of age) in the German cancer registry of the Robert-Koch-Institute (RKI) (12). The RKI registry is based on data of the German epidemiologic registries where all newly diagnosed cancer diseases are reported and the incidence is calculated.

EXOME SEQUENCING AND VARIANT CLASSIFICATION. Exome sequencing was performed in 14 PPCM patients with a history of cancer, and in 6 PPCM patients without a history of cancer where appropriate blood samples were available. DNA was extracted from whole blood samples. DNA enrichment and library preparation was performed using the xGen Exome Research Panel (Integrated DNA Technologies, Inc., Coralville, Iowa). Sequencing was performed on an Illumina NextSeq 500 using the NextSeq 500/550 High Output v2 kit (Illumina, San Diego, California). Alignment to the reference genome build (GRCh37) was performed using megSAP, version 0.1-710-g52d2b0c (Institute of Medical Genetics and Applied Genomics, University of Tübingen, Tübingen, Germany). Variant prioritization and visualization was performed with GSvar, version 2018_04, Integrated Genomics Viewer (13), version 2.4.14 and with Alamut visual, version 2.11 (Interactive Biosoftware, Rouen,

ABBREVIATION AND ACRONYMS

ATM = ataxia telangiectasia mutated

BMBF = Bundesministerium für Bildung und Forschung

BRCA1 = breast cancer 1

CPS = cancer predisposition syndrome

DCM = dilated cardiomyopathy

DDR = DNA damage response

DFG = Deutsche Forschungsgesellschaft

ERCC5 = excision repair cross-complementing rodent repair deficiency

FANCA = Fanconi anemia, complementation group

FKRP = fukutin-related protein

HCM = hypertrophic cardiomyopathy

HTX = heart transplantation

LVAD = left ventricular assist device

LVEF = left ventricular ejection fraction

PPCM = peripartum cardiomyopathy

RECQL4 = ATP-dependent DNA helicase Q4

RYR1 = ryanodine receptor 1

SLX4 = structure-specific endonuclease subunit SLX4

TXNRD2 = thioredoxin reductase 2

VUS = variants of unknown significance

TABLE 1 Clinical Presentation at Diagnosis and Follow-Up in PPCM Patients With and Without Cancer Diagnosis

	All PPCM (N = 236)	No Prevalent Cancer (n = 215)	Cancer Before or After PPCM Diagnosis (n = 21)	Cancer Before PPCM Diagnosis (n = 12)
Age at index, yrs	34 ± 5 (n = 236)	34 ± 5 (n = 215)	34 ± 5 (n = 21)	33 ± 6 (n = 12)
Parity SSP	1 (0–8) (n = 223)	1 (0–8) (n = 204)	1 (1–5) (n = 19)	1 (1–3) (n = 10)
Twin pregnancy	17 (35/212)	16 (31/193)	21 (4/19)	30 (3/10)
Caesarean section	70 (142/202)	70 (128/182)	70 (14/20)	82 (9/11)
Pregnancy-induced hypertensive disorders	39 (88/227)	40 (83/206)	24 (5/21)	17 (2/12)
Baseline LVEF, %	28 ± 10 (n = 236)	28 ± 10 (n = 215)	29 ± 9 (n = 21)	31 ± 10 (n = 12)
Follow-up LVEF, %	50 ± 11 (n = 165)	51 ± 11 (n = 145)	46 ± 10 (n = 20)*	43 ± 7 (n = 12)†
Beta-blocker, %	91 (207/228)	91 (188/207)	90 (19/21)	92 (11/12)
ACE inhibitor, ARB, %	95 (214/226)	95 (196/206)	90 (18/20)	91 (10/11)
Bromocriptine, %	78 (175/224)	79 (161/203)	67 (14/21)	75 (9/12)
Severe heart failure during follow-up, %	15 (27/175)	14 (21/154)	29 (6/21)	25 (3/12)
HTX/LVAD/death during follow-up, %	6 (10/175)	6 (9/154)	5 (1/21)	0 (0/12)
Full recovery at follow-up, %	53 (92/175)	55 (84/154)	38 (8/21)	17 (2/12)‡

Values are mean ± SD, mean (range), or % (n/N). The exact number of datasets analyzed for each parameter is provided in parentheses after each of the values. Baseline refers to time of PPCM diagnosis. Follow-up after PPCM in Table 1 was 7 ± 2 months with regard to follow-up LVEF. Severe heart failure at follow-up is defined as LVEF ≤35%, HTX, LVAD, or death during follow-up. Full-recovery at follow-up is defined as LVEF ≥50%. None of these patients experienced an abortion, miscarriage, or still birth. Comparison between the 2 groups (PPCM with cancer vs. PPCM without cancer) was performed using the Student's *t*-test for Gaussian distributed data and the Mann-Whitney *U* test where at least 1 column was not normally distributed. Categorical variables are presented as frequencies (proportions) and compared using Fisher exact tests. *$p < 0.05$ PPCM patients with cancer vs. PPCM patients without cancer; †$p < 0.01$ and ‡$p < 0.05$ PPCM patients with cancer prior PPCM vs. PPCM patients without cancer.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HTX = heart transplantation; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; PPCM = peripartum cardiomyopathy.

France). Variants were classified according to the criteria proposed by the American College of Medical Genetics and Genomics (ACMG) (14), and 248 genes were analyzed per patient. Genes associated with DCM were selected using the human phenotype ontology database (15) term "dilated cardiomyopathy" (HP:0001644; 115 genes); genes associated with DNA damage response (DDR) and general CPSs were composed of all genes listed in a benchmark study regarding cancer predisposition gene testing in adult patients (16) (Supplemental Tables 1 and 2). Only genetic variants which were classified as ACMG class III (variants of unknown significance) or likely pathogenic/pathogenic (ACMG class IV/V), thus inducing nonsense, missense, or frameshift mutations, were considered.

STATISTICAL ANALYSIS. Statistical analysis of the clinical data was performed using GraphPad Prism version 5.0a for Mac OS X (GraphPad Software, San Diego, California). Normal distribution was tested using the D'Agostino normality test. Continuous data were expressed as mean ± SD or median (range), according to normality of distribution. Comparison between the groups was performed using Student's *t*-test for Gaussian distributed data and the Mann-Whitney *U* test where at least 1 column was not normally distributed. Categorical variables are presented as frequencies (proportions) and compared using Fisher exact tests. The incidences of cancer in PPCM patients and the RKI registry were compared using 2-tailed chi-square test and odds ratios (ORs). Distribution in the 3 different subgroups depending on the cardiac status was compared using the chi-square test. All p values are 2-sided, and a p value of <0.05 was considered to be significant.

RESULTS

HIGH CANCER PREVALENCE IN PPCM PATIENTS, CLINICAL CHARACTERISTICS, AND OUTCOME. A total of 236 patients from German and Swedish PPCM cohorts (211 German and 25 Swedish patients) with a confirmed PPCM diagnosis and clinical history of either a confirmed presence or absence of a cancer diagnosis were included in the study. As both collectives were comparable regarding their characteristics and clinical data at baseline and over 7 ± 2 months follow-up, the data were pooled (**Table 1**). A history of cancer before PPCM or a cancer diagnosis after PPCM was identified in 21 of 236 (8.9%) PPCM patients over a median follow-up time of 33 months (range 5 months to 19 years). The cancer prevalence was 8.1% (17 of 211 patients) in the German cohort and 16% (4 of 25 patients) in the Swedish cohort. In comparison, the RKI registry (12) displayed a cancer prevalence of 0.59% in German women aged 0 to 49 years, indicating a 16-fold higher risk of cancer in this PPCM cohort compared to age-matched women without PPCM (OR: 16.4; 95% confidence interval [CI]: 10.5 to 25.7; $p < 0.001$). There were 23 cancer diagnoses in 21 patients. One patient (Patient #11) developed 2 different forms of cancer before PPCM and 1 patient (Patient #9) developed cancer both

TABLE 2 Age at Tumor and PPCM, Baseline and Follow-Up LVEF, Anticancer Treatment, and Genetic Variants in PPCM Patients With Cancer Before PPCM

Patient #	Tumor Diagnosis	Age at Tumor Diagnosis (yrs)	Age at PPCM (yrs)	Baseline LVEF	Follow-Up LVEF	Anticancer Therapy	Genetic Variant (P/LP/VUS)
01	Breast cancer	26	28	34	45	Chemotherapy (cyclophosphamide, doxetaxel, doxorubicin), surgery, radiation	**DSP (P)** DSG2 (VUS)
02	Breast cancer	37	40	35	46	Antihormone therapy, surgery, radiation	**CPT2 (P)**
03	Hodgkin lymphoma	26	38	26	50	Chemotherapy (bleomycin, cyclophosphamide, doxorubicin, etoposide, procarbazine, vincristine), radiation	BRCA1 (VUS)
04	Non-Hodgkin lymphoma	20	24	30	30	Chemotherapy (doxorubicin), radiation	TTN (VUS)
05	Acute myeloid leukemia	13	34	45	45	Chemotherapy (cytarabine, daunorubicin, doxorubicin, vincristine), radiation	MYBPC3 (VUS)
06	Osteosarcoma	10	23	27	47	Chemotherapy (cisplatin, methotrexate)	**MYH7 (LP)** **SLX4 (LP)**
07	Osteosarcoma	11	35	45	47	Chemotherapy unknown composition	**2 variants in RECQL4 (LP/LP)** 2 variants in FANCA (VUS/VUS)
08	Melanoma	33	39	15	33	Surgery	none
09	Hodgkin lymphoma	17	36	40	45	Radiation	**TTN (P)** **ATM (P)** **ERCC5 (P)**
10	Non-Hodgkin lymphoma	35	40	32	54	Chemotherapy (adriamycin, cyclophosphamide, rituximab, vincristine)	TTN (VUS)
11	Acute lymphatic leukemia + melanoma	4	31	20	36	Chemotherapy (daunorubicin, doxorubicin)	TXNRD2 (VUS) ATM (VUS)
12	Acute lymphatic leukemia	4	29	20	35	Chemotherapy (adriamycin, dexamethasone, 6-mercaptopurin, methotrexate, vincristine), radiation	Not performed

Cardiac function at the time of diagnosis (baseline) and follow-up after PPCM in PPCM patients with malignancies before PPCM. Variants identified by exome sequencing are presented with their corresponding American College of Medical Genetics and Genomics class. All LP/P variants are in **bold**.

ATM = TM serine/threonine kinase; BRCA1 = breast cancer gene 1; CPT2 = carnitine-palmitoyltransferase II; DSG2 = desmoplakin; ERCC5 = excision repair cross-complementation group 5; FANCA = Fanconi anemia, complementation group; HTX = heart transplantation; LP = likely pathogenic; LVEF = left ventricular ejection fraction; MYBPC3 = cardiac myosin binding protein C; MYH7 = myosin heavy chain 7; P = pathogenic; PPCM = peripartum cardiomyopathy; RECQL4 = ATP-dependent DNA helicase Q4; SLX4 = structure-specific endonuclease subunit SLX4; TTN = titin; TXNRD2 = thioredoxin reductase 2; VUS = variant of unknown significance.

before (Hodgkin's lymphoma) and after PPCM (breast cancer) (Tables 2 and 3).

OUTCOME OF PPCM PATIENTS WITH CANCER BEFORE PPCM. Cancer occurred in 5.1% (12 of 236 patients) of patients before their diagnosis of PPCM (age range at PPCM diagnosis: 19 to 45 years) which is 9-fold higher compared to age-matched females in the RKI registry (women aged 0 to 49 years had a cancer risk of 0.59%; OR: 9.0; 95% CI: 5.0 to 16.1). Of the patients with cancer before PPCM, 92% (11 of 12 patients) had undergone cancer therapy and/or radiation (Tables 1 and 2). To understand whether anticancer treatment may have induced heart failure before pregnancy, all 11 cases of patients treated with drug therapy and/or radiation were re-evaluated regarding the differential diagnosis of cardiomyopathy induced by cardiotoxic cancer therapy and signs of heart failure before pregnancy. None of 11 patients reported any signs of heart failure after cancer therapy and prior to pregnancy. At baseline, all PPCM patients with and without cancer displayed a similar LVEF, but at 7 ± 2 months follow-up, the mean LVEF was significantly lower in all PPCM patients with a history of cancer (Table 1). In addition, fewer patients with a cancer diagnosis before PPCM displayed full cardiac recovery at follow-up compared with patients with no cancer history (Figure 1, Table 1).

PREVALENCE AND OUTCOME OF PPCM PATIENTS WITH A CANCER DIAGNOSIS AFTER PPCM. In 207 PPCM patients (age range 20 to 50 years), clinical follow-up data after diagnosis were available for a median of 33 months (range 5 months to 19 years). Of those, 4.83% (10 of 207) patients developed cancer after PPCM, with 1 patient having had a different cancer diagnosis before PPCM (Tables 2 and 3). Compared with the cancer prevalence in women of the same age group (RKI women aged 0 to 49 years: 0.59%), PPCM patients had a 9-fold higher risk for cancer after PPCM (OR: 8.5; 95% CI: 4.5 to 16.1). For all patients with cancer after PPCM, LVEF at the time of PPCM diagnosis, after cancer diagnosis, and after cancer therapy were available (Table 3). One patient with a prolactinoma diagnosed shortly after PPCM diagnosis did not obtain the recommended anticancer treatment with a prolactin blocker and required HTX 3 months after PPCM diagnosis (Table 3). A second patient diagnosed with prolactinoma was treated with the prolactin blocker bromocriptine and

TABLE 3 Age at Tumor Diagnosis and PPCM, Baseline LVEF at PPCM Diagnosis, LVEF After Anticancer Treatment, and Genetic Variants in PPCM Patients With Cancer After PPCM

Patient #	Tumor Diagnosis	Age at Tumor Diagnosis (yrs)	Age at PPCM	Baseline LVEF	LVEF After Cancer Therapy	Anticancer Therapy	Genetic Variant (P/LP/VUS)
09	Breast cancer	48	36	40	46	Antihormone therapy, surgery, radiation	**TTN (P)** **ATM (P)** **ERCC5 (P)**
13	Breast cancer	44	40	24	52	Chemotherapy (paclitaxel), antihormone therapy, surgery, radiation	TTN (VUS) POLD1 (VUS)
14	Breast cancer	37	36	20	59	Chemotherapy (paclitaxel, carboplatin), surgery	**TTN (LP)** **NBN (P)**
15	Colorectal cancer	33	31	30	60	Surgery	Not performed
16	Prolactinoma	30	30	12	HTX	No antitumor therapy	Not performed
17	Ovarian cancer	36	31	29	55	Surgery	RYR1 (VUS)
18	Microprolactinoma	31	31	30	58	No antitumor therapy but bromocriptine	Not performed
19	Cervical cancer	45	39	30	50	Surgery	Not performed
20	Breast cancer	51	39	22	50	Chemotherapy: tamoxifen; radiation; surgery	Not performed
21	Cervical cancer	41	40	32	55	Surgery	Not performed

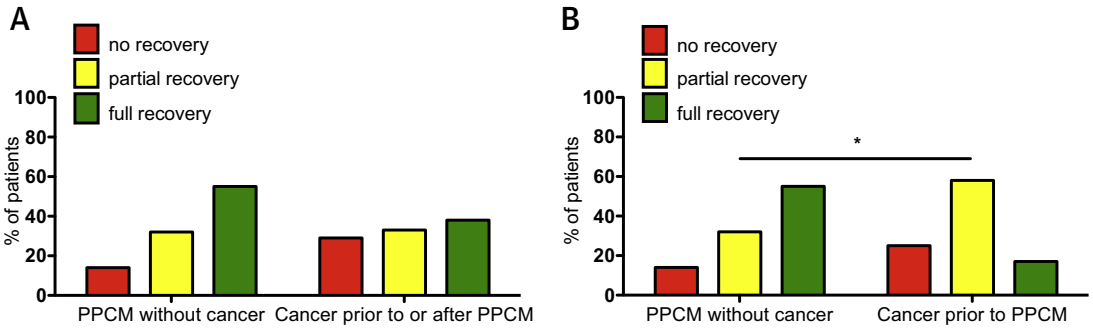
Cardiac function at the time of diagnosis and after cancer therapy in PPCM patients with malignancies after PPCM. PPCM patient 9 had Hodgkin lymphoma before PPCM and breast cancer after PPCM (see Table 2). Variants identified by exome sequencing are presented with their corresponding American College of Medical Genetics and Genomics class. All LP/P variants are in **bold**.

ATM = TM serine/threonine kinase; ERCC5 = excision repair cross-complementation group 5; HTX = heart transplantation; LP = likely pathogenic; LVEF = left ventricular ejection fraction; NBN = nibrin; P = pathogenic; POLD1 = polymerase delta 1; PPCM = peripartum cardiomyopathy; RYR1 = ryanodine receptor 1; TTN = titin; VUS = variant of unknown significance.

recovered (Table 3). A patient with Hodgkin lymphoma treated with radiation therapy before PPCM and also treated for breast cancer with antihormone therapy, radiation, and surgery after PPCM was in moderate heart failure after the second cancer and corresponding treatment (Tables 2 and 3). The 7 remaining patients displayed normal LV function after cancer diagnosis and treatment; none developed acute heart failure while undergoing anticancer therapy after PPCM, and none received anthracycline-based chemotherapies (Table 3).

EXOME SEQUENCING REVEALS THE PRESENCE OF GENE VARIANTS ASSOCIATED WITH CARDIOMYOPATHY AND A HIGHER CANCER RISK IN PPCM PATIENTS WITH CANCER. Exome sequencing was performed in a subset of 14 PPCM patients: 10 had developed cancer before and 3 after the onset of PPCM, and 1 patient developed cancer before and after PPCM (Tables 2 and 3). In 13 of 14 patients (93%), either pathogenic (P, class V), likely pathogenic (LP, class IV) variants, and/or variants of unknown significance (VUS, class III) associated with DCM/HCM and/or CPS were

FIGURE 1 Cardiac Status at 7 ± 2 Months Follow-Up in PPCM Patients Stratified According to Cancer Diagnosis



Cardiac status at 7 ± 2 months follow-up in PPCM patients stratified according to cancer diagnosis. Comparison of cardiac status at 7 ± 2 months follow-up in PPCM patients without cancer and with cancer before and after PPCM **(A),** and in PPCM patients who had cancer before PPCM **(B). Red column** = nonrecovery (LVEF ≤35%, HTX, LVAD implantation, or death); **yellow column** = partial recovery (LVEF >35% to 49%); **green column** = full recovery (LVEF ≥50%). The p values were calculated using chi square test; *$p < 0.05$. HTX = heart transplantation; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; PPCM = peripartum cardiomyopathy.

detected. Forty-three percent (6 of 14 patients) carried only LP and P variants in DCM/HCM and/or CPS (**Table 2** and **3**). All gene variants were either missense, frameshift, or nonsense mutations; an overview of all variant details including full gene names, sequence information, and variant frequency in the general population according to the gnomAD database (17) is presented in Supplemental Table 3. In 11 patients, VUS and P/LP variants associated with cardiomyopathy were found in 8 genes (*CPT2*, *DSG2*, *DSP*, *MYBPC3*, *MYH7*, *RYR1*, *TTN*, and *TXNRD2*). Five patients carried LP/P variants in *CPT2*, *DSP*, *MYH7,* or *TTN* and in 7 patients, 7 VUS were identified in *DSG2*, *MYPBC3*, *RYR1*, *TTN,* and *TXNRD2* (**Tables 2** and **3**). One patient with cancer before PPCM carried an LP/P in DSP and a VUS variant in DSG2 (**Table 2**).

In 7 of 14 patients, VUS and LP/P gene variants associated with CPS were found in 8 different genes (*ATM, BRCA1, ERCC5, FANCA, NBN, POLD1, RECQL4,* and *SLX4*), with all affected genes involved in DDR (18–22). Four of 14 patients carried LP/P variants in *ATM, ERCC5, NBN, RECQL4,* and *SLX4* (**Tables 2 and 3**). One patient was compound heterozygous for 2 different LP variants in *RECQL4* and also for 2 different rare *FANCA* VUS (**Table 2**). Five patients carried VUS or LP/P gene variants associated with DCM and CPS. Within this group, 3 patients were identified with only LP/P variants in DCM/HCM and in CPS genes, including the patient with cancer before and after PPCM (only P gene variants in *TTN*, *ATM*, and *ERCC5*), 1 patient with cancer before PPCM (LP gene variants in *MYH7* and in *SLX4),* and 1 patient with cancer after PPCM (LP gene variant in *TTN* and P gene variant in *NBN*) (**Tables 2 and 3**).

PRESENCE OF GENE VARIANTS ASSOCIATED WITH CARDIOMYOPATHY AND/OR A HIGHER CANCER RISK IN PPCM PATIENTS WITHOUT A CANCER DIAGNOSIS. Whole-exome sequencing in 6 PPCM patients with no history of cancer revealed that 1 patient carried a P variant in the FKRP gene leading to Emery Dreyfuss muscular dystrophy associated with cardiomyopathy (23), 1 patient carried a VUS in MYH7, and 1 patient carried a VUS in TTN and another VUS in E-Cadherin 1 (CDH1) (Supplemental Table 4). CDH1 is a CPS gene associated with cell-to-cell interaction (24). No DDR-associated gene variants were detected in these patients.

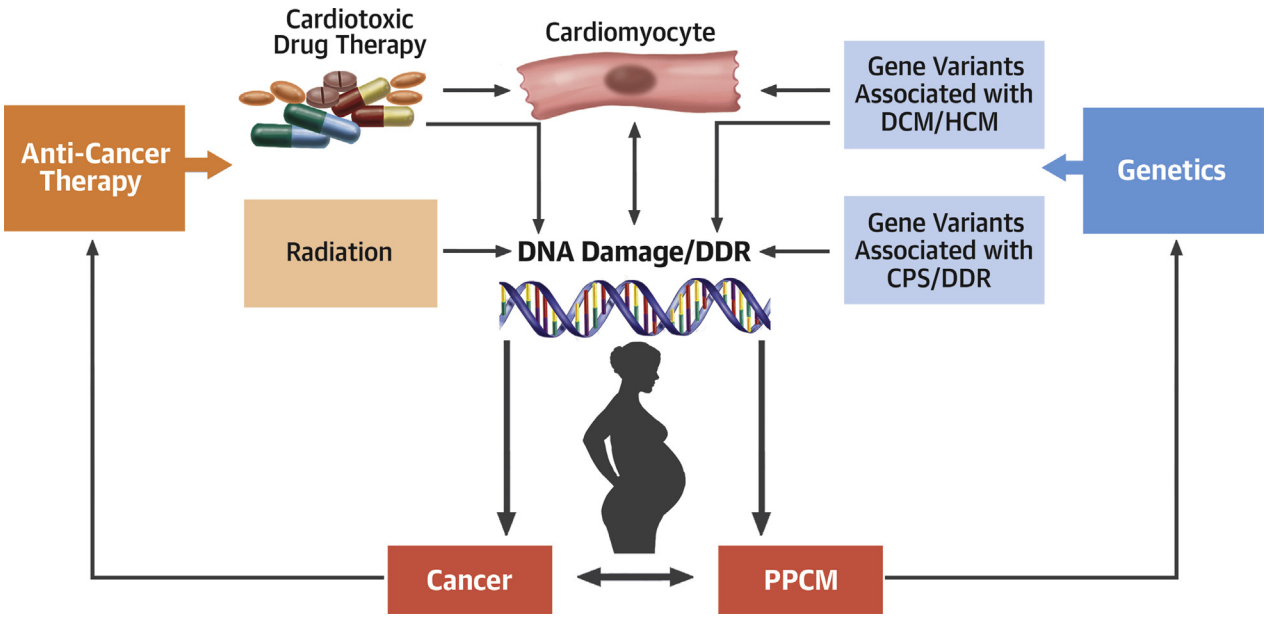
DISCUSSION

The present study reports a 16-fold higher prevalence of early-onset cancer in PPCM patients from 2 European PPCM cohorts compared to the cancer risk in age-matched women without PPCM (**Central Illustration**). The risk for cancer before PPCM was 9-fold and for cancer after PPCM was also 9-fold higher compared to age-matched women without PPCM. It has been reported that pregnancy before the age of 30 years decreases the risk for breast cancer (25), whereas pregnancy after the age of 35 years may increase slightly (by 0.041%) the risk for breast cancer in the first 5 postpartum years (26). Adding the slightly increased cancer risk after pregnancy in older women to the general risk (0.59%) of women age 0 to 49 years, the risk of cancer for older postpartum women is estimated to be 0.63%. The average age of patients with cancer after PPCM was 35 years at the time of PPCM diagnosis, suggesting that this group may have a slightly increased cancer risk compared to women without late pregnancies. However, as 4.83% of PPCM patients developed cancer after PPCM, the risk for cancer when calculated on the 0.63% cancer risk for women with pregnancies after the age of 35 years in this subgroup is still 8-fold higher compared to age-matched postpartum women without PPCM. Taken together, PPCM patients in the German and Swedish cohorts have a markedly increased risk for cancer both before and after PPCM compared to the cancer risk of age-matched women without PPCM.

Cardiac function at the time of PPCM diagnosis was comparable across the entire cohort, but the rate of full recovery was lower in PPCM patients with cancer before PPCM compared with PPCM patients with no cancer history before PPCM. In patients with cancer before PPCM, cancer was detected mostly during childhood or adolescence with the majority undergoing anticancer treatments including potentially cardiotoxic drug therapy (anthracyclines, other cytotoxic antibiotics, alkylating agents, antimetabolites, or antimicrotubule agents) and/or radiation. Cancer therapy–induced cardiotoxicity can manifest both short-term and later in life (27–30). None of the PPCM patients with cancer before PPCM reported short-term or long-term cardiotoxic effects in response to anticancer treatment, suggesting that pregnancy may have induced PPCM as a form of late cardiotoxicity.

A recent study has shown that patients with rare gene variants associated with DCM/HCM have a higher risk for cardiomyopathies induced by cancer therapy (31). In our cohort, we detected P, LP, or VUS in 93% of all genotyped PPCM patients with cancer. Of those, 100% (10 of 10 patients) undergoing cardiotoxic cancer therapy before PPCM carried at least 1 VUS or LP/P gene variant associated with DCM/HCM and/or CPS/DDR, and one-half of them carried LP/P

CENTRAL ILLUSTRATION **Potential Connections Among Cancer, Cancer Therapies, and the Genetic Predisposition for Cardiomyopathy and Cancer in PPCM Patients**



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DNA damage plays a central role in the development of cancer and also contributes to the development of heart failure. Mutations associated with cardiomyopathy render the heart more sensitive to stress induced by cardiotoxic treatment and pregnancy. Therefore, patients with mutations associated with DDR have a significantly elevated risk of developing cancer. Exposure to cardiotoxic cancer therapy, which either alone or in combination with mutations associated with DCM/HCM increases the risk for developing PPCM. Furthermore, heart failure may promote early onset cancer in CPS mutation carriers and thereby can explain, at least in part, the higher cancer risk in patients after PPCM. CPS = cancer predisposition syndrome; DCM = dilated cardiomyopathy; DDR = DNA damage response; HCM = hypertrophic cardiomyopathy; PPCM = peripartum cardiomyopathy.

variants. These observations suggest that genetic predisposition for DCM/HCM and CPS may sensitize to PPCM, especially in combination with previous cardiotoxic cancer therapy.

Among the mutated genes associated with DCM/HCM were *TTN* and *MYH7* variants, which had previously been associated with PPCM (32). Additional mutations were discovered in *CPT2* and *DSP*. *CPT2* deficiency impairs long-chain fatty-acid oxidation leading to liver failure with hypoketotic hypoglycemia, cardiomyopathy, seizures, and early death as severe forms, and exercise-induced muscle pain and weakness, sometimes associated with myoglobinuria in milder forms (33). Heterozygotes are usually asymptomatic, but manifesting heterozygous carriers have also been reported (33). *DSP* is an important component of desmosomes, which are dynamic junctions between cells that maintain the structural integrity of skin and heart tissues by withstanding shear forces (34). In the present study, we found cardiomyopathy-associated LP/P gene variants also in a PPCM patient without cancer (a P variant in the *FKRP* gene leading to Emery Dreyfuss muscular dystrophy which is known to also affect the heart) (23) with a similar frequency (approximately 15%) as reported in other PPCM collectives (32). Whereas there was a tendency for such mutations to be present in PPCM with cancer, this should be addressed in larger PPCM collectives in the future.

All PPCM patients with cancer were diagnosed before the age of 49 years, and therefore are classified as early-onset cancer, which is more likely to be associated with CPS, especially when mutations in DDR genes can be identified (35–37). One-half of the sequenced PPCM patients with cancer carried gene variants associated with CPS (19,38,39), a finding that had not been documented in PPCM patients. All CPS-associated gene variants discovered in PPCM patients with cancer mapped to genes involved in the DDR,

that is, in *ATM, BRCA1, ERCC5, FANCA, NBN, POLD1, RECQL4,* and *SLX4* (18–22) with LP/P variants in either ATM, ERCC5, RECQL4, SLX4, and/or NBN. Importantly, *ATM, ERCC5, SLX4*, and *NBN* variants are associated with an increased risk for breast and/or ovarian cancer (19,38–40). Both cancer forms were present in one-third of the present PPCM cohort. The patient with the compound heterozygous *RECQL4* variants had a reported body height of only 154 cm and was diagnosed with osteosarcoma, with a likely diagnosis of a very rare, *RECQL4*-associated CPS (RAPADILINO syndrome [OMIM-P: 266280], Rothmund-Thomson syndrome [OMIM-P: 268400]). Unfortunately, this patient was lost to follow-up, so further symptoms of *RECQL4*-associated CPS (skin changes, and skeletal abnormalities) could not be evaluated. In contrast to the PPCM patients with cancer, none of the 6 sequenced PPCM patients without cancer carried DDR-associated gene variants suggesting that the exclusive presence of mutations in DDR genes in PPCM patients with cancer (acknowledging small numbers in each group) might indicate a connection between DDR gene variants, PPCM, and cancer. Along this line, gene variants associated with impaired DDR may affect the stress tolerance and repairability of the heart, a notion supported by the observation that mutations in *ATM* and *BRCA1* not only increase the risk for cancer, but may also promote cardiomyopathies and heart failure (41–43). In addition, BRCA mutation carriers displayed an increased risk for anthracycline-induced cardiotoxicity (41). Alternatively, DDR mutations may lead to a better efficacy of chemotherapy, as, for example, cancer patients with systemic loss of function mutations in DDR genes have a better survival rate after platinum-based chemotherapy (44). Thereby, DDR mutations may allow patients with childhood cancer to be healed from cancer but may also increase the risk for a subsequent PPCM. Additional studies and longer follow-up data will be required to analyze the impact of DDR mutations with respect to PPCM complicated by cancer. In this regard, comparison of whole-exome sequencing data of childhood cancer survivors with and without subsequent PPCM could provide insights whether the prevalence of DDR associated mutations in PPCM may predispose only for early-onset cancer or for both diseases.

Our findings showing a high prevalence of CPS-associated gene variants are also interesting in light of a hypothesis put forward by a previous study which suggested that heart failure might promote a malignant transformation of pretumor stages and the progression of tumor disease (7). A possible explanation is that PPCM patients with cancer after PPCM had an existing genetic risk for early-onset cancer, and heart failure in PPCM may have induced cancer. We also observed that common PPCM risk factors such as pre-eclampsia are less frequent in PPCM patients with cancer, supporting the hypothesis that cancer-associated risk factors, such as cardiotoxic cancer therapies and/or genetic predisposition, are causally linked with PPCM and represent a subset of PPCM different than that triggered by hypertensive disorders of pregnancy.

STUDY LIMITATIONS. In addition to the limited sample size, the follow-up data (average age at diagnosis: 34 years) available in this study ranged between 5 months and 19 years after PPCM diagnosis, with an average of 33 months follow-up. It is possible that the risk for cancer in PPCM patients is underestimated in this study and is increased for a wider subset than that observed in our cohorts.

CONCLUSIONS

This study is the first to describe a markedly increased risk for malignancies both before and after the diagnosis of PPCM. The type of cancer, the cancer therapy, and/or gene variants associated with DCM/HCM and/or with CPS/DDR may connect PPCM and cancer. Therefore, pre-pregnancy echocardiographic screening and counseling, together with close monitoring during pregnancy and postpartum, may be recommended for patients with a history of cancer and cancer therapy before pregnancy. In addition, as PPCM patients may have a higher (genetic) risk of developing cancer, they may require both regular cardiovascular and cancer screening as well as genetic screening for both diseases. In the future, questionnaires for medical history for cancer disease and whole-exome sequencing should be performed in large registries such as the EURObservational Research Program (45) or the investigations of pregnancy-associated cardiomyopathy registry (NCT01085955) (46) to confirm and further define the connection between PPCM and cancer risk.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The present study highlights a high cancer prevalence in PPCM patients which is associated with CPS/DDR and/or DCM/HCM gene variants. These observations suggest that genetic screening for cancer and cardiomyopathy may be advisable for PPCM patients. In addition, the study indicates a higher risk of PPCM in cancer patients with exposure to potentially cardiotoxic cancer therapies, even in the absence of short-term clinical cardiotoxicity. Our findings suggest cancer patients should undergo pre-pregnancy echocardiographic screening and counseling, as well as close monitoring during pregnancy and in the first months postpartum. Furthermore, PPCM patients should undergo not only cardiovascular monitoring, but also regular cancer screening.

TRANSLATIONAL OUTLOOK: Further research in larger independent PPCM cohorts is needed to confirm both the higher prevalence of cancer in PPCM patients as well as the higher risk for PPCM as a late form of cardiotoxicity after cancer treatment. Moreover, experimental studies are needed to determine the potential pathologic impact of systemic DNA damage mutations (CPS/DDR) not only for cancer but also for the development of PPCM. It is important to understand whether DCM/HCM mutations leading to PPCM may also promote the early-onset cancer after PPCM.

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APPENDIX **For supplemental tables, please see the online version of this paper.**