Published in final edited form as:
Int J Cancer. 2012 October 15; 131(8): 1904–1911. doi:10.1002/ijc.27443.

Malignant melanoma, breast cancer and other cancers in patients with Parkinson's disease

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Abstract

Previous studies report an atypical cancer pattern among patients with Parkinson's disease. Here, we evaluate the cancer pattern among people diagnosed with Parkinson's disease in an extension of our previous cohort study. For this Danish population-based cohort study, we identified 20,000 people with Parkinson's disease diagnosed in 1977–2006, from the National Danish Hospital Register. Cohort members were followed up for cancer in the Danish Cancer Registry until December 31, 2008, and their incidence rates of cancer were compared to age-, sex- and calendar period-specific rates in the general population as standardized incidence rate ratios (SIRs). In subanalyses, we estimated the risk for cancer among patients with early onset Parkinson's disease and we also compared breast tumor characteristics among women with Parkinson's disease to that of a control group. The overall cancer risk in our cohort was decreased [SIR = 0.86; 95% confidence interval (CI) = 0.83–0.90], as were those for smoking-related (SIR = 0.65; 95% CI = 0.60–0.70) and nonsmoking-related cancers (SIR = 0.79; 95% CI = 0.71–0.86). The cohort had increased risks for malignant melanoma (SIR = 1.41; 95% CI = 1.09–1.80), nonmelanoma skin cancer (SIR = 1.29; 95% CI = 1.18–1.39) and female breast cancer (SIR = 1.17; 95% CI = 1.02–1.34). Among patients with early onset Parkinson's disease, the risk for cancer was comparable to that of the general population. Of breast tumor characteristics, only grade of malignancy differed between Parkinson's disease women and controls. This study confirms a lower cancer risk among people with Parkinson's disease. Increased risks for malignant melanoma, nonmelanoma skin cancer and breast cancer might be due to shared risk factors with Parkinson's disease.

Keywords

Parkinson's disease; cancer; population-based cohort; Denmark

As early as 1954, it was reported that people with Parkinson's disease have fewer cancers than the general population.[1] This association has since been the subject of several studies, all but one[2] of which found an overall decrease in the risk for cancer both before[3-8] and after diagnosis of Parkinson's disease.[6,7,9-14] The observed low cancer risk has been suggested to be due to a high proportion of nonsmokers among people with this disease[15]; however, the risks for some cancers unrelated to smoking have also been found to be lower.[6,10]

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Cancers reported to be more common among people with Parkinson's disease are malignant melanoma and other skin cancers,[9,10,16-18] as confirmed in a recent meta-analysis.[19] Moreover, an excess risk for female breast cancer was reported in some,[12-14] but not all, studies.[5,7] Various causal mechanisms have been proposed to explain these links between Parkinson's disease and cancers; however, the available evidence is weak.[20]

To address the intriguing link between Parkinson's disease and cancer, we extended our follow-up for cancer of a large cohort of people with Parkinson's disease in Denmark with 8 years and included an additional 6,000 patients with Parkinson's disease. Furthermore, in this report, we include risk estimates for cancer in patients with early onset Parkinson's disease and we also compare tumor characteristics among breast cancer cases to those of a control group.

Material and Methods

The study cohort has been described in detail elsewhere.[14] Briefly, patients with Parkinson's disease were identified from the files of the Danish Hospital Register, information on all persons admitted to nonpsychiatric hospitals since 1977,[21] and the information on outpatients was added to the Register on January 1, 1995. The information includes the personal identification number of the patient, the dates of admission or first contact and discharge or last contact, a code for the primary diagnosis made at the hospital and codes for up to 19 supplementary diagnoses. The personal identification number, which is unique to every Danish citizen, incorporates sex and date of birth and permits accurate linkage among registers. The diagnoses are coded according to the Danish version of the *International Classification of Diseases*, 8th revision (ICD-8) until the end of 1993 and the 10th revision (ICD-10) thereafter.

We identified 21,656 patients with a primary diagnosis of Parkinson's disease (ICD-8 code 342; ICD-10 code G20) in the Danish Hospital Register during the period January 1, 1977, to December 31, 2006. Of these, we excluded eight who were citizens of Greenland and 73 who were below the age of 35 years at the time of first diagnosis of Parkinson's disease. We also excluded 81 patients with dementia (ICD-8: 290.09–290.19; 293.09, ICD-10: F00–F03; F05.1; G30) and 720 with cerebrovascular disease (ICD-8: 430–438, ICD-10: I60–I69; G45; G46) diagnosed between 1977 and 3 years before the first diagnosis of Parkinson's disease, as these patients were likely to have secondary Parkinson's disease caused by arteriosclerotic brain damage or Lewy body dementia. Finally, we excluded 431 patients who died before discharge from hospital, yielding a final study population of 20,343, of whom 10,712 (53%) were men and 9,631 (47%) were women. Patients who had a cancer diagnosis prior to their Parkinson's disease diagnosis were included in the cohort.

The cohort members were linked to the Central Population Register for information on vital status and migration and to the Danish Cancer Registry to ascertain incident cases of cancer (both in situ and invasive), subsequent to entry into the cohort, up to the end of 2008.[22] The Danish Cancer Registry has recorded incident cases of cancer on a nationwide basis since 1943 and has been shown to have accurate and almost complete ascertainment of cancer cases.[22] Follow-up for cancer started on the date of first hospital discharge or outpatient visit with a primary diagnosis of Parkinson's disease. For all cohort members, follow-up ended on the date of death (n = 15,020) or on December 31, 2008 (n = 5,323), whichever occurred first. Observed cancers were merged into a number of site-specific cancer groups on the basis of the general outline of ICD-10. For individuals who developed more than one primary cancer at the same site, only the first diagnosis was included in the analyses, whereas different primary cancers in the same individual were counted as separate cancers.

Analyses

The expected numbers of cancers were calculated by multiplying the number of person-years of cohort members by the sex-specific cancer incidence rates for the Danish inhabitants in 5-year-age groups and calendar periods of observation. Standardized incidence ratios (SIRs), serving as a measure of the relative risk for cancer, and 95% confidence intervals (CIs) were derived by assuming a Poisson distribution of the observed cancers.[23] In a subanalysis, cancers were grouped into either "smoking-related sites" or "other specified sites," as proposed by the International Agency for Research on Cancer.[24] To evaluate the impact of time since hospitalization for Parkinson's disease on the risk for cancer, we estimated risks for different lengths of time since hospitalization for Parkinson's disease for selected cancers. As the cancer pattern among patients with early onset Parkinson disease might be influenced by genetic factors of importance for development of this disease, we performed a sensitivity analysis of data on the 529 patients in whom Parkinson's disease was diagnosed when they were 35–49 years. We used SAS software version 9.1 for all analyses. The study protocol was approved by the Danish Data Protection Agency (no. 2002-41-2112).

Breast tumor characteristics

For each woman in the cohort registered with breast cancer in the Danish Cancer Registry, we sampled 10 women with breast cancer from the general population, matched to the patient on age and year of breast cancer diagnosis. Since 1977, information on treatment and tumor characteristics, including morphology and behavior, of most cases of breast cancer in Denmark have been registered in a database operated by the Danish Breast Cancer Cooperative Group (DBCG) of the Danish Surgical Society.[25] The female patients and comparison women were linked to the files of the DBCG database, and the χ^2 test was used to explore whether the tumors of the two groups of women differed with respect to morphology, grade of malignancy or overall receptor status.

Results

The average age of the cohort of 20,343 patients was 72.7 years at the time of first hospital or outpatient contact for a primary diagnosis of Parkinson's disease; 79% of the patients were born in 1929 or earlier. In total, 115,250 person-years of follow-up after diagnosis were accrued (mean, 5.7 years; range, 0–32 years); 16% of the patients were followed up for 10 years or more. Overall, 2,218 cancers were observed in the cohort, with 2567.4 expected, resulting in a SIR of 0.86 (95% CI = 0.83–0.90; Table 1). Malignant melanoma (SIR = 1.41; 95% CI = 1.09–1.80), nonmelanoma skin cancer (SIR = 1.29; 95% CI = 1.18–1.39) and female breast cancer (SIR = 1.17; 95% CI = 1.02–1.34) occurred more frequently in the cohort than in the general population. The overall reduction in cancer risk was mainly due to a strong decrease in the risk for smoking-related cancers (SIR = 0.65; 95% CI = 0.60–0.70) and to a smaller reduction in the risk for cancers at all other sites (SIR = 0.79; 95% CI = 0.71–0.86). In particular, reduced risks were seen for cancers of the larynx (SIR = 0.39), lung (SIR = 0.40) and urinary bladder (SIR = 0.48), types most strongly associated with which are the cancer tobacco smoking (Table 1).

The overall reduction in risk for cancer was larger in men (SIR = 0.81; 95% CI = 0.76–0.85) than in women (SIR = 0.94; 95% CI = 0.88–1.00), and some differences were seen for cancers at specific sites, including a markedly decreased risk of gall bladder cancer in women (SIR = 0.39; 95% CI = 0.12–0.90), but not men (SIR = 0.62; 95% CI = 0.20–1.45), and a markedly decreased risk of colorectal cancer in men (SIR = 0.77; 95% CI = 0.65–0.90), but not in women (SIR = 0.89; 95% CI = 0.75–1.04); however, the CIs were

overlapping. Men also had a lower risk for smoking-related cancers than women; however, the risks for nonsmoking-related cancers were similar for men and women (Table 2).

The risk estimates for malignant melanoma decreased with time after diagnosis of Parkinson's disease as did the risk estimates for nonmelanoma skin and smoking- and nonsmoking-related cancers. In contrary, the risk for female breast cancer increased with increasing time since hospitalization for Parkinson's disease (Table 3).

Of the 529 patients in whom Parkinson's disease was diagnosed before they were 50 years, 43 subsequently had cancer, yielding an overall SIR of 0.98 (95% CI = 0.71–1.32). The site-specific risk estimates for this group were unstable owing to small numbers. The three most frequent types of cancer were nonmelanoma skin (SIR = 1.77; 95% CI = 0.97–2.97, $n = 14$), female breast (SIR = 1.14; 95% CI = 0.46–2.34, $n = 7$) and colorectal cancer (SIR = 1.46; 95% CI = 0.54–3.19, $n = 6$). Malignant melanoma was diagnosed in one patient, whereas 1.7 was expected (SIR = 0.59; 95% CI = 0.01–3.26). The risks for both smoking-related cancers (SIR = 0.71; 95% CI = 0.38–1.22, $n = 13$) and nonsmoking-related cancers (SIR = 0.81; 95% CI = 0.32–1.66, $n = 7$) were decreased among patients with early=onset Parkinson's disease.

Information on the morphology and behavior of the breast cancers was available for 170 (77%) of 222 women with Parkinson's disease (two women had two breast cancers resulting in the 224 cases shown in Table 1) and for 1,439 (65%) of the 2,208 women of the population control group. We observed no difference in tumor morphology or overall estrogen receptor status. Although the distributions of grade of malignancy were different between the two groups, no pattern could be discerned; however, more patients with Parkinson's disease had tumors of unknown grade, and slightly more of patients with Parkinson's disease had Grade 1 tumors (Table 4).

Discussion

In this extension of our previous cohort study,[14] we found a 14% lower cancer risk among more than 20,000 patients with Parkinson's disease than in the general population. This overall finding was due to lower risks for both smoking- and nonsmoking-related cancers. In contrast, the risks for malignant melanoma, nonmelanoma skin cancer and female breast cancer were higher among these patients. Men with Parkinson's disease had an overall lower risk for cancer than women, and they also had a lower risk for smoking-related cancers. These gender differences in risk for cancers could be due to differences in smoking habits,[26] and biologic differences between men and women with Parkinson's disease[27] might also partly explain our results.

In accordance with our findings, all except one[6] previous study of malignant melanoma before or after Parkinson's disease showed an increased risk (Table 5). In our study, the risk estimate for malignant melanoma was lower than that in our previous study (SIR, 1.41 vs. 1.95),[14] because no increase in risk for malignant melanoma (SIR = 0.89; 95% CI = 0.55–1.37) was found among patients with Parkinson's disease in the most recent follow-up period (1999–2008). There are several explanations for this finding. One possibility is that the patients most recently found to have Parkinson's disease were less likely to get a diagnosis of malignant melanoma. Furthermore, few patients with Parkinson's disease were found to have malignant melanoma in the most recent period ($n = 21$), and we cannot exclude the possibility that this is a chance finding. As the risk estimates for malignant melanoma decreased with time after the diagnosis of Parkinson's disease, we considered that we captured most cases of melanoma, that is, those that occurred within the first 0–4 years after the onset of Parkinson's disease, which is the period of highest risk. Moreover, for

nonmelanoma skin cancer and smoking- and nonsmoking-related cancers, the risk decreased with time after hospitalization for Parkinson's disease. In contrary, the risk for female breast cancer increased with increasing time since hospitalization for Parkinson's disease. These findings are in agreement with our previous report[14]; however, we were unable to explain the positive association between risk for female breast cancer and time since hospitalization for Parkinson's disease.

The reasons for the consistent reported association between Parkinson's disease and an increased risk for malignant melanoma are unknown; however, common genetic components of the two diseases have been suggested.[29] A recent case–control study within the Health Professionals Follow-up Study and Nurses' Health Study showed an association between a genetic determinant of red hair (melanocortin1-receptor Cys/Cys variant) and a threefold increase in risk for Parkinson's disease.[30] This genetic determinant is also a risk factor for malignant melanoma.[31] Another report on data for the same cohorts showed that a family history of malignant melanoma in first-degree relatives was associated with an increased risk for Parkinson's disease (RR = 1.85; 95% CI = 1.2–2.8)[32]; however, we were unable to substantiate this finding in a recent cohort study,[33] in which the risk of parents and siblings of patients with early onset malignant melanoma (before 50 years) for Parkinson's disease was no higher than that of the general population (hospitalization rate ratio = 1.14; 95% CI = 0.9–1.5). Differences in the etiology of malignant melanoma and early onset malignant melanoma might explain the differences in the results of these two studies.[34] Paisan-Ruiz and Houlden[35] recently suggested that Parkinson's disease and malignant melanoma are linked through the tyrosine pathway. This pathway is crucial for both dopamine and melanin syntheses, and they hypothesized that the reduction in dopamine production that occurs in Parkinson's disease causes changes in the tyrosine pathway that lead to increased production of melanin, predisposing the person to malignant melanoma.[36]

Exposure to solar radiation is associated with increased risks for malignant melanoma and nonmelanoma skin cancer[37]; and even though it is unlikely that people with Parkinson's disease are more heavily exposed to solar radiation than the general population, we cannot exclude that exposure to solar radiation play a role in the observed increased risk for malignant melanoma.

The results of studies on breast cancer before and after a diagnosis of Parkinson's disease is less consistent (Table 5). It is known that a higher cumulative exposure of breast tissue to estrogens increases the risk for breast cancer[38]; however, it has also been suggested that estrogens are neuroprotective and may protect against Parkinson's disease.[39] This has been proposed as an explanation for the lower prevalence of Parkinson's disease among women.[40] On the basis of these arguments, we would expect to find an inverse relation between Parkinson's disease and breast cancer; however, we found the opposite. Although one small study from Japan also reported an increased risk for breast cancer among patients with Parkinson's disease,[12] none of the other previous studies showed an association (Table 5). It is likely that the observed increase in risk for breast cancer of patients with Parkinson's disease is due to factors other than estrogen. The *ATM* (ataxia telangiectasia mutated) gene has been associated with both Parkinson's disease and breast cancer.[41] Mice deficient in this gene showed greater degeneration of dopaminergic neurons than mice with the gene.[42] The association between the *ATM* gene and breast cancer has been examined in studies of the risk for breast cancer of people with a high probability of mutations in this gene, that is, blood relatives of patients with ataxia telangiectasia. Relatives were consistently found to be at increased risk for breast cancer, with risk estimates ranging from 1.7 to 5.1.[43-45] Mutations in the *PARKIN* gene[46] and in the tumor-suppressing gene *PTEN*[47] have also been suggested to be involved in both cancer and Parkinson's disease.

Increased levels of transcript of genes associated with neurodegeneration have been found in estrogen- and progesterone receptor-negative breast tumors, whereas genetic variants associated with cell proliferation were found in estrogen- and progesterone receptor-positive tumors.[48] Our comparison of the characteristics of breast tumors from women with Parkinson's disease and control women did not confirm these differences in receptor status, although we did observe a difference in the grade of malignancy at the time of diagnosis of Parkinson's disease, these patients had more Grade 1 tumors.

We also evaluated the risk for cancer of patients with early onset Parkinson's disease, diagnosed when they were 35–49 years, as they may have a stronger genetic predisposition to the disease.[49] The overall risk for cancer of this subgroup was similar to that of the general Danish population and thus generally higher than that of patients in whom Parkinson's disease began after they were 50 years. For smoking-related and nonsmoking-related cancers, we observed decreased risks among patients with early onset Parkinson's disease, with risk reductions similar to those observed for the whole cohort. The risk estimates for early onset Parkinson's disease was based on small numbers and do not allow firm conclusions.

Smoking is inversely associated with Parkinson's disease[50]; however, this association might only partly explain the overall decrease in cancer risk seen in this study, as the risk for other cancers was lower. The decreased risk for cancer among patients with Parkinson's disease may be explained by multiple factors including the presence of certain genes and smoking or other environmental factors influencing the risk of both Parkinson's disease and cancer.[51]

Our study has many strengths, including the large number of patients with Parkinson's disease diagnosed during a 30-year period and access to unbiased complete data from the Danish Cancer Registry and the Danish Hospital Register. Furthermore, information from the DBCG allowed us to compare the characteristics of the breast tumors in the women in our cohort with those of a control group. One limitation of our study is the lack of diagnostic details on patients with Parkinson's disease; however, we included only patients with a primary diagnosis of this disease. Furthermore, we had no information on lifestyle factors of importance for cancer risk, such as tobacco smoking, alcohol use and diet. We were also unable to exclude the possibility of surveillance bias and the fact that the physical and, for some patients, mental consequences of Parkinson's disease might have masked symptoms of cancer. Patients with less severe disease might not have been included in our cohort, as patients treated exclusively within the primary healthcare system are not included in the Danish Hospital Register.

In summary, our results confirm the association between Parkinson's disease and malignant melanoma and indicate a link with breast cancer. Genetic and environmental factors might partly explain our findings; however, the specific factors that cause the atypical cancer pattern of patients with Parkinson's disease remain to be elucidated.

Acknowledgments

The authors thank Andrea Bautz, Danish Cancer Society Research Center, for performing the statistical analyses. They also thank the Danish Breast Cancer Cooperative Group (DBCG) for providing the data on breast tumor characteristics.

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Table 1

Standardized incidence ratios (SIRs) for total and site-specific cancers (1977–2008) among 20,343 patients with a primary diagnosis of Parkinson's disease in the period 1977–2006

Site of cancer (ICD-10)	Observed	Expected	SIR	95% CI
All sites	2,218	2567.4	0.86	0.83–0.90
All sites except nonmelanoma skin	1,632	2111.8	0.77	0.74–0.81
Skin (C43, C44 and C460)	651	501.6	1.30	1.20–1.40
Malignant melanoma (C43)	65	46.0	1.41	1.09–1.80
Nonmelanoma (C44 and C460)	586	455.6	1.29	1.18–1.39
Female breast (C50)	224	190.9	1.17	1.02–1.34
All smoking-related sites	785	1211.1	0.65	0.60–0.70
Larynx (C32)	7	17.8	0.39	0.16–0.81
Lung (C33, C34 and C39)	122	306.1	0.40	0.33–0.48
Urinary bladder (C67)	77	160.3	0.48	0.38–0.60
Ovary, fallopian tube and broad ligament (C56 and C570–C574)	23	36.3	0.63	0.40–0.95
Colorectal (C18–C21)	294	356.6	0.82	0.73–0.92
Other smoking-related sites[1]	262	334.0	0.78	0.69–0.89
Nonsmoking-related sites[2]	438	558.1	0.79	0.71–0.86
Prostate (C61)	183	246.5	0.74	0.64–0.86
Non-Hodgkin lymphoma (C82–C85 and C883–C889)	39	53.6	0.73	0.52–0.99
Corpus uteri (C54, C55 and C58)	37	45.1	0.82	0.58–1.13
Brain (C71 and C751–C753)	31	31.5	0.99	0.67–1.40
Multiple myeloma (C90 and C880–C882)	23	30.1	0.76	0.48–1.15
Lymphatic leukemia (C91)	23	34.9	0.66	0.42–0.99
Other nonsmoking-related sites[2,3]	102	116.4	0.88	0.72–1.06
Ill-defined and unspecified sites (C76–C80)	120	105.5	1.14	0.94–1.36

[1] Buccal cavity and pharynx (C00–C14 and C462), esophagus (C15), stomach (C16), liver (C22), pancreas (C25), cervix uteri (C53), kidney (C64), renal pelvis and ureter (C65–C66) and myeloid leukemia (C92).

[2] Except malignant melanoma, nonmelanoma skin, female breast and ill-defined and unspecified sites.

[3] Small intestine (C17), gall bladder (C23–C24), heart and mediastinum (C380–C383 and C388), pleura (C384 and C450), bones (C40–C41), mesothelium and connective tissue (C451–C459; C461; C463; C467; C468; C469; C47–C49; B210), male breast (C50), external female genital organs (C51–C58), testis (C62), eye (C69), endocrine glands (C73–C74, C750 and C754–C759), Hodgkin lymphoma (C81), monocytic leukemia (C93), other and unspecified leukemia (C94–C95) and other and unspecified cancer in lymphatic and hematopoietic tissue (C96).

Table 2

Standardized incidence ratios (SIRs) with corresponding 95% confidence intervals (CIs) for all sites combined and for selected individual sites in 10,712 men and 9,631 women with a primary diagnosis of Parkinson's disease in Denmark, 1977–2006

	Men			Women		
Site of cancer (ICD-10)	**Obs.**	**SIR**	**95% CI**	**Obs.**	**SIR**	**95% CI**
All sites	1,166	0.81	0.76–0.85	1,052	0.94	0.88–1.00
Malignant melanoma (C43)	34	1.40	0.97–1.96	31	1.42	0.97–2.02
Nonmelanoma skin (C44 and C460)	327	1.28	1.14–1.43	259	1.30	1.14–1.46
All smoking-related sites	438	0.60	0.55–0.66	347	0.72	0.64–0.80
Buccal cavity and pharynx (C00–C14 and C462)	17	0.62	0.36–0.99	11	0.82	0.41–1.48
Stomach (C16)	33	0.81	0.56–1.13	17	0.70	0.41–1.12
Colorectal (C18–C21)	144	0.77	0.65–0.90	150	0.89	0.75–1.04
Liver (C22)	16	0.99	0.57–1.61	8	0.85	0.36–1.67
Lung (C33, C34 and C39)	77	0.37	0.29–0.46	45	0.46	0.34–0.62
Urinary bladder (C67)	61	0.49	0.37–0.63	16	0.45	0.26–0.73
Myeloid leukemia (C92)	13	0.95	0.50–1.62	4	0.41	0.11–1.04
Other smoking-related sites[1]	77	0.79	0.62–0.98	96	0.76	0.62–0.93
Nonsmoking-related sites[2]	309	0.80	0.72–0.90	129	0.77	0.64–0.91
Gallbladder and biliary tract (C23–C24)	5	0.62	0.20–1.45	5	0.39	0.12–0.90
Brain (C71 and C751–C753)	20	1.15	0.70–1.77	11	0.79	0.39–1.41
Non-Hodgkin lymphoma (C82–C85 and C883–C889)	22	0.76	0.48–1.15	17	0.69	0.40–1.10
Multiple myeloma (C90 and C880–C882)	15	0.86	0.48–1.41	8	0.63	0.27–1.25
Lymphatic leukemia (C91)	15	0.71	0.40–1.18	8	0.58	0.25–1.14

Site of cancer (ICD-10)	Men			Women		
	Obs.	SIR	95% CI	Obs.	SIR	95% CI
Other nonsmoking-related sites[2]	232	0.80	0.70–0.91	80	0.88	0.70–1.09

[1] Esophagus, pancreas, larynx, cervix uteri, ovary, fallopian tube and broad ligament, kidney, renal pelvis and ureter.

[2] Except malignant melanoma, nonmelanoma skin, female breast and ill-defined and unspecified sites.

Table 3

Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) for selected types of cancer among patients with Parkinson's disease

Years since first hospitalization for Parkinson's disease	SIR (95% CI); number of observed cases					
	All sites combined	Malignant melanoma	Nonmelanoma skin	Female breast	Smoking-related cancers[1]	Nonsmoking-related cancers[2]
<1	1.03 (0.9–1.1); *n* = 410	1.20 (0.5–2.4); *n* = 8	1.28 (1.0–1.6); *n* = 85	1.25 (0.9–1.8); *n* = 33	0.80 (0.7–0.9); *n* = 154	1.18 (1.0–1.4); *n* = 103
1–4	0.88 (0.8–0.9); *n* = 1059	1.71 (1.2–2.4); *n* = 36	1.33 (1.2–1.5); *n* = 280	1.06 (0.9–1.3); *n* = 91	0.70 (0.6–0.8); *n* = 403	0.74 (0.6–0.9); *n* = 194
5–9	0.78 (0.7–0.9); *n* = 511	1.49 (0.9–2.4); *n* = 18	1.28 (1.1–1.5); *n* = 153	1.17 (0.9–1.5); *n* = 60	0.51 (0.4–0.6); *n* = 155	0.71 (0.6–0.9); *n* = 99
≥10	0.76 (0.7–0.9); *n* = 238	0.49 (0.1–1.4); *n* = 3	1.14 (0.9–1.4); *n* = 68	1.46 (1.0–2.0); *n* = 40	0.52 (0.4–0.7); *n* = 73	0.66 (0.5–0.9); *n* = 42
p for trend	<0.0001	0.21	0.39	0.33	<0.0001	<0.0001

[1] Buccal cavity and pharynx, esophagus, stomach, colorectal, liver, pancreas, larynx, lung, cervix uteri, ovary, fallopian tube and broad ligament, kidney, renal pelvis and ureter and urinary bladder and myeloid leukemia.

[2] Except melanoma, nonmelanoma skin, female breast and ill-defined and unspecified sites.

Table 4

Characteristics of breast cancer tumors among women with both Parkinson's disease and breast cancer and controls with breast cancer (data from the Danish Breast Cancer Cooperative Group)

	Patients with Parkinson's disease (%), *n* = 170	Controls (%), *n* = 1,439	*p*-value
Morphology			
Ductal	110 (64.7)	1,062 (73.8)	0.16
Lobular	20 (11.8)	170 (11.8)	
Subtypes of invasive ductal carcinoma	11 (6.5)	86 (6.0)	
Adenoid, secretory, apocrine, metaplastic, paget, fibroadenoma and other	5 (2.9)	16 (1.1)	
Unknown	24 (14.1)	105 (7.3)	
Grade of malignancy			
Grade I	52 (46.0)	345 (31.3)	0.008
Grade II	40 (35.4)	518 (46.9)	
Grade III	19 (16.8)	203 (18.4)	
Unknown	59 (34.7)	373 (25.9)	
Overall estrogen receptor status			
Negative	18 (10.6)	200 (13.9)	0.36
Positive	106 (62.4)	923 (64.1)	
Unknown	46 (27.1)	316 (22.0)	

Table 5

Studies on associations between Parkinson's disease and malignant melanoma and Parkinson's disease and breast cancer

Study type	Author	Location	Sex	Cases among patients with Parkinson's disease	RR	95% confidence interval
Malignant melanoma before Parkinson's disease						
Case–control	Elbaz *et al.*[5]	USA	M + F	3	1.50	0.25–8.98
	Olsen *et al.*[8]	Denmark	M + F	46	1.44	1.03–2.01
	Driver *et al.*[4]	USA	M	3	1.62	0.27–9.83
	Lo *et al.*[7]	USA	M + F	6	1.5	0.40–5.2[1]
Cohort	Fois *et al.*[6]	United Kingdom	M + F	9	0.5	0.2–0.9[2]
Malignant melanoma after Parkinson's disease						
Case–control	Becker *et al.*[9]	United Kingdom	M + F	9	2.72	0.66–11.12[3]
	Lo *et al.*[7]	USA	M + F	14	1.6	0.71–3.60[1]
Cohort	Jansson and Jankovic[11]	USA	M + F	2	$p = 0.04$	
	Constantinescu *et al.*[17]	USA	M + F	5	3.3	1.1–7.8
	Driver *et al.*[10]	USA	M	9	6.15	1.77–21.37
	Olsen *et al.*[28]	Denmark	M + F	48	1.85	1.37–2.46
	Bertoni *et al.*[16]	USA	M + F	10	2.24	1.21–4.17
	Inzelberg *et al.*[18]	Israel	M + F	20	4.4	2.6–7.6
Breast cancer before Parkinson's disease						
Case–control	Elbaz *et al.*[5]	USA	M + F	1	0.20	0.02–1.71
	D'Amelio *et al.*[3]	Italy	M + F	3	NS	NS
	Olsen *et al.*[8]	Denmark	F	134	1.09	0.90–1.33
	Lo *et al.*[7]	USA	M + F	11	0.72	0.27–1.9[1]
Cohort	Fois *et al.*[6]	United Kingdom	M + F	133	0.9	0.7–1.0[2]
Breast cancer after Parkinson's disease						
Case–control	Becker *et al.*[9]	United Kingdom	M + F	19	0.92	0.47–1.80[3]

Study type	Author	Location	Sex	Cases among patients with Parkinson's disease	RR	95% confidence interval
	Lo *et al.*[7]	USA	M + F	11	0.95	0.38–2.4[1]
Cohort	Minami *et al.*[12]	Japan	F	3	5.49	1.10–16.03
	Olsen *et al.*[14]	Denmark	F	142	1.24	1.0–1.5
	Fois *et al.*[6]	United Kingdom	M + F	21	0.7	0.4–1.0[2]

Abbreviations: RR: relative risk; NS: not specified.

[1]Adjusted for age, sex, smoking, alcohol consumption and BMI. Malignant melanoma additionally adjusted for eye color.

[2]Adjusted for age (5-year bands), sex, time period in single calendar years and district of residence.

[3]Adjusted for age, sex, calendar time, BMI and smoking status.