

Cancer risk in oil refinery workers: a pooled mortality study in Italy

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SUMMARY

Background: Oil refinery workers are exposed to several well-established carcinogens and working in this type of industry has been classified by IARC as probable carcinogen to humans (Group 2A). **Objectives:** To examine the mortality experience of workers employed in four Italian oil refineries. **Methods:** The cohort included 5112 male workers ever employed between 1949 and 2011. The average follow-up period was 49 years. Standardized mortality ratios (SMR) and 95% Confidence Intervals (CI) were calculated using as reference age-gender-calendar specific regional rates. Analyses by duration of employment and latency were performed. **Results:** In the whole cohort, pleural cancer (6 deaths, SMR 1.59; 95% CI 0.71-3.53), brain cancer (14 deaths, SMR 1.47; 95% CI 0.87-2.49) and lymphatic leukemia (LL) (8 deaths, SMR 1.81; 95% CI 0.91-3.62) showed increased risks. All pleural cancers occurred after 10 years of latency and the highest risk was observed among workers with duration ≥ 20 years; the brain cancer excess was confined in the shortest duration and latency. The LL (and chronic lymphatic leukemia in particular) excess regarded workers with latency and duration longer than 20 years. Four deaths from acute myeloid leukemia (AML) were observed and all occurred after 20 years of latency (SMR 1.55, 95% CI 0.58-4.12); a two-fold-increased risk was observed in the longest duration. No increased risk for skin cancer has been observed in our study population. **Conclusion:** Our findings are consistent with recent evidence of an increased mortality from pleural and hematopoietic malignancies (AML and LL) among oil refinery workers. However, the lack of individual quantitative exposure data and the small number of observed events prevent the identification of the possible causal role of individual chemicals, including benzene, especially at the current very low exposure levels.

RIASSUNTO

«**Rischio di cancro nei lavoratori addetti alla raffinazione di petrolio: uno studio di mortalità in impianti italiani**». **Introduzione:** I lavoratori dell'industria petrolchimica sono esposti a numerosi noti agenti cancerogeni e l'attività lavorativa in questo settore è stata definita come probabilmente cancerogena per l'uomo dalla IARC (Gruppo 2A). **Obiettivo:** Studiare la mortalità causa specifica nei lavoratori di quattro raffinerie italiane. **Metodi:** La coorte

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allo studio è composta da 5112 lavoratori maschi, impiegati tra il 1949 e il 2011, seguiti nel tempo per un follow-up medio pari a 49 anni. Sono stati calcolati i Rapporti Standardizzati di Mortalità (SMR) con i relativi Intervalli di Confidenza (IC) al 95% utilizzando tassi regionali specifici per età e genere. È stata poi effettuata l'analisi per latenza e durata dell'esposizione per selezionate cause di morte. **Risultati:** Nell'intera coorte si è osservata una mortalità aumentata per mesotelioma pleurico (6 decessi, SMR 1.59; IC 95% 0.71–3.53), tumore al cervello (14 decessi, SMR 1.47; IC 95% 0.87–2.49) e leucemie linfatiche (LL) (8 decessi, SMR 1.81; IC 95% 0.91–3.62). Tutte le morti per tumore della pleura si sono verificate dopo oltre 10 anni di latenza e in lavoratori con durata dell'esposizione ≥ 20 anni, mentre quelle per tumori cerebrali si sono verificati in lavoratori con latenza e durata dell'esposizione < 10 anni. I casi di LL (di tipo cronico in particolare) hanno riguardato lavoratori con latenza e durata esposizione ≥ 20 anni. Sono stati osservati 4 casi fatali di leucemia mieloide acuta (LMA), tutti nel gruppo con latenza ≥ 20 anni (SMR 1.55, IC 95% 0.58–4.12); un incremento di due volte nella mortalità è emerso tra i lavoratori con oltre 20 anni di durata dell'esposizione. Non è stato osservato nessun aumento di rischio per tumore alla cute. **Conclusione:** I nostri risultati sono coerenti con le recenti evidenze di un aumento di mortalità per mesotelioma e tumori emopoietici (LL e LMA) nei lavoratori dell'industria petrolchimica. Tuttavia, il ridotto numero di casi osservati e la scarsità di dati quantitativi di esposizione non permettono di identificare in modo univoco il ruolo dell'esposizione a benzene nel determinare il rischio, soprattutto alle attuali basse dosi.

INTRODUCTION

The oil refinery industry employs hundreds of thousands of workers worldwide with exposure to several well-established human carcinogens such as benzene, untreated or mildly treated mineral oils, polycyclic aromatic compounds, several metals (including arsenic, lead, chromium, nickel) and asbestos. In 1989, the International Agency for Research on Cancer (IARC), evaluated working in petroleum refineries as “probably carcinogenic to humans (Group 2A)”. This limited evidence applied to skin cancer and leukemia (7).

Subsequent to IARC evaluation, several epidemiological studies focused on cancer mortality among petrolchemical workers and reported increased risks for additional cancer sites. An extensive systematic review of those studies was conducted by Wong and Raabe separately for solid tumors (23) and lymphohemopoietic cancers (16, 24). Analyzing about 350,000 workers from US, Canada, Europe and Australia, the authors did not observe an increase in mortality from specific cancer sites with the only possible exception of skin cancer (pooled RR=1.10, 95% CI 0.99–1.22).

Benzene could contribute to increase cancer risk in the oil refinery industry. Benzene occurs naturally at small concentrations in gasoline and is also added to unleaded gasoline for its anti-knock properties. In 2009, IARC updated its evaluation of benzene

carcinogenicity (1, 8): in addition to the well-known association with acute myeloid leukemia (AML), the IARC Working Group examined the results of numerous epidemiological studies and concluded for a limited evidence of an increase in risk of acute and chronic lymphatic leukemia (ALL, CLL), non-Hodgkin lymphoma (NHL) and multiple myeloma (MM).

Following the updated IARC classification of benzene, a few studies investigated in more detail the risk of hematopoietic malignancies among oil refinery workers, focusing on the different subtypes, with conflicting results. In 2011, an extensive meta-analysis of occupational cohort studies (21) reported evidence for an association between occupational exposure to benzene and risk of MM, ALL, and CLL, which was more pronounced in follow-up studies starting after 1970 and in studies reporting an elevated risk of AML (considered as a proxy of good methodological quality, due to its well-known association with benzene exposure). On the other hand, the association with risk of non Hodgkin's lymphoma (NHL) was unclear.

Khalade et al (11) in a meta-analysis of 15 studies found evidence of an increased risk of AML and CLL, but no association between benzene exposure and CML risk.

Koh and colleagues (12) investigated the mortality of a large cohort of workers employed at one refinery and six petrochemical plants in Korea. In-

creased risks for leukemia and lymphohematopoietic cancers were observed in production workers. An increased incidence of NHL was observed in an Italian cohort study of petrochemical workers (3): the excess was mainly concentrated in workers of the vinyl chloride monomer production plant.

A pooled analysis of three case-control studies with well documented low exposure to benzene, failed to show a dose-response relationship for both AML and CLL, suggesting that previous evidences might have been related to higher exposures or to more complex exposure-patterns (17).

A few studies focused on asbestos exposure among petrochemical workers, and showed an increased risk of pleural mesothelioma, particularly among maintenance workers (6, 13, 15, 18, 20). Positive associations were found in two large cohorts in Canada (35,000 workers, SMR=8.6 among maintenance workers) (13) and USA (10,000 workers, SMR for maintenance workers=4.7) (20). Conflicting findings have been found among petrochemical workers in Italy, and in particular among maintenance workers. Maintenance activities often involve direct contact with asbestos in Italian oil refineries. (3, 6, 15).

To contribute to quantify occupational cancer risk in oil refinery workers, we conducted a large mortality cohort study by pooling four Italian cohorts with more than 5,000 workers followed up for a long period of time.

In this paper, we present results on the mortality experience of the whole cohort, which includes a plant that was previously investigated (2, 5) and whose follow-up has now been extended.

METHODS

Study population

The overall cohort included 5112 male workers ever employed between 1949 and 2011 in four oil refineries in Northern (Milano, Cremona) and Central Italy (Cagliari, Rome).

Information on date of birth, residence, date of hire and duration of employment was abstracted for each study subject from the companies' personnel records.

Vital status was ascertained through the vital statistical offices of the town of the subjects' last residence. For deceased subjects, death certificates were obtained and coded according to standard rules following the International Classification of Diseases in use at the time of death and then converted to the ICD-9 revision codes.

Cohort members contributed to the person-years from the beginning of employment in the plant until exit from the study (because of death, emigration, or loss to follow-up), or until the end of the study period.

Statistical Analysis

We calculated cause-specific Standardized Mortality Ratios (SMR), and 95% confidence intervals (CI), as the ratio of observed and expected deaths using the mortality rates specific by age, gender, and calendar years (1970-2012) of the regions where the plants were located as reference. Italian rates were used for the years 1949-1969, when regional rates were unavailable. We explored cause-specific mortality by duration of employment (0-9, 10-19, 20 or more years), time since first employment (i.e. latency: 0-9, 10-19, 20 or more years) and period of employment (≤ 1969 , 1970-1979, ≥ 1980).

Duration of employment was lagged 10 years for all plants (5), to overcome the lack of information about occupational history between 1982 and 1992 in one plant (Milano) in the last 10 years before cessation of activity.

We used Poisson regression modeling with an internal reference in the analysis of duration and latency.

RESULTS

The main characteristics of the four cohorts are reported in table 1. Subjects contributed to a total of 143,303 person years. The average follow-up length was 49 years. Vital status ascertainment was successful for 98.5% of the workers. Cause of death was unknown for 66 (1.3%) subjects; we included these deaths in the overall mortality but not in the analysis of cause-specific mortality.

Mortality by specific cause of death is reported in table 2. Overall mortality was lower than expected,

Table 1 - Main characteristics of the four sub-cohorts under investigation

Oil refinery plant	Number of subjects	Period of employment	Follow-up period, mean duration	Deaths		Lost to follow-up	
				N	(%)	N	(%)
Milano	1583	1949-1982	1949-2006, 57Y	670	(42%)	21	(1.3%)
Cremona	903	1961-2010	1961-2011, 50Y	196	(22%)	22	(2.6%)
Roma	676	1965-1982	1965-2006, 41Y	142	(21%)	7	(1.0%)
Cagliari	1950	1964-2011	1964-2012, 48Y	152	(8%)	25	(1.3%)
Total	5112		(49 years)	160	(23%)	75	(1.5%)

Table 2 - Mortality results by specific cause of death

Cause of death (ICD-9 code)	Deaths	SMR	95%CI
All causes (000-989)	1160	0.81	0.77-0.86
All cancers (140-239)	454	0.87	0.79-0.95
Digestive tract cancers (150-159)	153	0.82	0.70-0.96
Stomach (151)	41	0.85	0.62-1.16
Colon (153)	28	0.91	0.63-1.32
Rectum (154)	13	0.96	0.56-1.66
Liver (155)	30	0.71	0.50-1.02
Pancreas (157)	22	0.97	0.64-1.48
Lung (162)	139	0.86	0.72-1.01
Pleural (163)	6	1.59	0.71-3.53
Skin (172-173)	3	0.55	0.18-1.70
Prostate (185)	20	0.75	0.48-1.16
Bladder (188)	17	0.86	0.54-1.39
Brain (191,225)	14	1.47	0.87-2.49
Lymphatic and Hematopoietic (200-208)	41	1.16	0.86-1.58
Lymphoma (200,202)	17	1.13	0.70-1.82
Hodgkin's Disease (201)	4	1.35	0.51-3.60
non-Hodgkin's Lymphoma (202)	13	1.08	0.62-1.85
Multiple Myeloma (203)	3	0.51	0.16-1.57
Leukemia (204,208)	21	1.41	0.92-2.17
Myeloid leukemia	8	1.28	0.64-2.56
Acute myeloid leukemia (AML)	4	1.23	0.46-3.27
Chronic myeloid leukemia (CML)	3	1.33	0.43-4.10
Lymphatic leukemia	8	1.81	0.90-3.62
Chronic lymphatic leukemia (CLL)	6	1.63	0.73-3.62
Acute lymphatic leukemia (ALL)	0	-	-
Cardiovascular diseases (390-458)	339	0.70	0.63-0.78
Respiratory diseases (460-519)	49	0.59	0.44-0.78
Digestive tract diseases (520-579)	57	0.55	0.42-0.71
Genito-urinary tract diseases (580-629)	10	0.62	0.33-1.15
Accidents (800-999)	72	0.71	0.57-0.90

SMR: Standardized Mortality Ratio; CI: Confidence interval

mainly because of a marked reduction of mortality from cardiovascular, respiratory, digestive and genito-urinary diseases. All cancer mortality was also lower

than expected. As regard specific cancer deaths, we did not observe any significant excess risk; deaths were slightly above the expectation for pleural can-

cer (6 deaths, SMR=1.59, 95% CI 0.71-3.53), and brain cancer (14 deaths, SMR=1.47, 95% CI 0.89-2.49). We did not observe an increase in mortality from lymphohemopoietic neoplasms; deaths from lymphatic leukemia (LL, 8 deaths, SMR=1.81, 95% CI 0.91-3.62), myeloid leukemia (ML, 8 deaths, SMR=1.28, 95% CI 0.64-2.56), and Hodgkin Lymphoma (HL, 4 deaths, SMR=1.35, 95% CI 0.51-3.60) were non significantly above the expectation.

Table 3 and 4 show results by time since first employment and duration of employment for cancers with at least 4 deaths.

Five out of the six cases of pleural cancer occurred more than 20 years since starting employment (table 3) yielding a 71% increased risk (95% CI 0.71-4.11). The increase in brain cancer mortality was confined to the shortest latency category and was not affected by duration of employment.

Among hematopoietic neoplasms, AML and CLL showed a 55% and 78% excess after 20 years since first employment. All cases of AML occurred in workers with 20 or more years of latency.

No clear pattern by duration of employment was observed for most cancer deaths with three possible exceptions: 3 AML deaths yielded a two-fold increased risk in workers employed 20 or more years; in the same category of duration of employment excess risks were observed for LL (5 deaths, SMR 2.59 95% CI 1.08-6.22, 4 of them were CLL) and pleural cancer (4 deaths, SMR 2.36 95% CI 0.89-6.29).

Analysis by period of employment (≤ 1969 , 1970-1979, ≥ 1980 , Supplementary table 1) did not show any particular trend for most of the relevant cause of deaths.

Table 3 - Standardized mortality ratios (SMR) and 95% Confidence Intervals (CI) for selected cancer causes by time since first employment

Cause of death	Time since first employment (years)					
	<10		10-19		20 +	
	Deaths	SMR (95%CI)	Deaths	SMR (95%CI)	Deaths	SMR (95%CI)
All cancers	19	0.68 (0.43-1.07)	61	0.90 (0.71-1.17)	374	0.87 (0.79-0.97)
Stomach	1	0.31 (0.04-2.20)	10	1.29 (0.69-2.39)	30	0.81 (0.57-1.16)
Colon	0	-	4	3.30 (0.45-3.23)	24	0.93 (0.62-1.38)
Rectum	0	-	1	1.71 (0.08-4.15)	12	1.09 (0.62-1.92)
Liver	0	-	2	0.48 (0.12-1.93)	28	0.77 (0.53-1.12)
Pancreas	0	-	2	0.75 (0.19-3.01)	20	1.05 (0.68-1.63)
Lung	8	1.07 (0.53-2.13)	21	1.00 (0.65-1.53)	110	0.82 (0.68-0.99)
Pleural	0	-	1	2.49 (0.35-17.7)	5	1.71 (0.71-4.11)
Skin	0	-	0	-	3	0.71 (0.23-2.21)
Prostate	0	-	1	0.56 (0.08-3.98)	19	0.80 (0.51-1.25)
Bladder	0	-	2	1.05 (0.26-4.20)	15	0.90 (0.54-1.49)
Brain	4	4.28 (1.61-11.4)	2	1.13 (0.28-4.54)	8	1.17 (0.59-2.35)
Lymphoma	1	0.56 (0.08-3.94)	2	0.87 (0.22-3.47)	14	1.28 (0.76-2.17)
HD	0	-	2	2.51 (0.62-10.0)	2	1.49 (0.37-5.96)
NHL	1	1.02 (0.14-7.21)	0	-	12	1.25 (0.71-2.21)
Leukemia	1	0.64 (0.09-4.54)	4	1.81 (0.68-4.82)	16	1.44 (0.88-2.36)
Myeloid leukemia	0	-	1	1.07 (0.15-7.62)	7	1.49 (0.71-3.12)
AML	0	-	0	-	4	1.55 (0.58-4.12)
CML	0	-	1	2.39 (0.34-17.0)	2	1.27 (0.32-5.05)
Lymphatic leukemia	0	-	1	1.85 (0.26-13.1)	7	1.98 (0.94-4.15)
CLL	0	-	1	1.87 (0.26-13.3)	5	1.78 (0.74-4.28)

Table 4 - Standardized mortality ratios and 95% Confidence Interval (CI) for selected cancer causes by duration of employment

Cause of death	Duration of employment (years)					
	<10		10-19		20 +	
	Deaths	SMR (95%CI)	Deaths	SMR (95%CI)	Deaths	SMR (95%CI)
All cancers	124	0.80 (0.67-0.95)	123	0.87 (0.73-1.05)	207	0.91 (0.80-1.05)
Stomach	11	0.67 (0.37-1.21)	11	0.77 (0.42-1.38)	19	1.10 (0.70-1.71)
Colon	9	1.04 (0.54-2.00)	5	0.63 (0.26-1.52)	14	0.91 (0.59-1.68)
Rectum	3	0.73 (0.24-2.26)	5	1.32 (0.55-3.17)	5	0.89 (0.37-2.15)
Liver	3	0.27 (0.09-0.85)	8	0.79 (0.40-1.58)	19	0.90 (0.58-1.42)
Pancreas	3	0.48 (0.15-1.50)	5	0.84 (0.35-2.02)	14	1.34 (0.79-2.26)
Lung	43	0.91 (0.68-1.23)	39	0.89(0.65-1.22)	57	0.80 (0.61-1.03)
Pleural	2	1.55 (0.39-6.20)	0	-	4	2.36 (0.89-6.29)
Skin	0	-	2	1.43 (0.36-5.73)	1	0.44 (0.06-3.17)
Prostate	7	0.98 (0.47-2.06)	3	0.42 (0.13-1.29)	10	0.81 (0.44-1.50)
Bladder	5	0.91 (0.38-2.19)	7	1.34 (0.64-2.81)	5	0.56 (0.23-1.33)
Brain	7	1.99 (0.95-4.18)	2	0.80 (0.20-3.21)	5	1.42 (0.60-3.43)
Lymphoma	6	1.07 (0.48-2.38)	4	1.14 (0.43-3.03)	7	1.18 (0.56-2.48)
HD	2	1.15 (0.29-4.58)	2	3.05 (0.76-12.2)	0	-
NHL	4	1.04 (0.39-2.76)	2	0.70 (0.17-2.80)	7	1.31 (0.62-2.74)
Leukemia	7	1.32 (0.63-2.78)	3	0.83 (0.27-2.57)	11	1.85 (1.03-3.34)
Myeloid leukemia	3	1.37 (0.44-4.25)	0	-	5	1.98 (0.82-4.75)
AML	1	0.95 (0.13-6.73)	0	-	3	2.05 (0.66-6.36)
CML	2	2.30 (0.57-9.19)	0	-	1	1.34 (0.17-8.80)
Lymphatic leukemia	1	0.72 (0.10-5.12)	2	1.81 (0.45-7.23)	5	2.59 (1.08-6.22)
CLL	1	0.78 (0.11-5.56)	1	1.16 (0.16-8.24)	4	2.58 (0.97-6.87)

DISCUSSION

In our mortality study of a pooled cohort of Italian oil refinery workers followed-up for about 50 years, we observed an increased mortality from brain, pleural and some hematopoietic cancers.

The observed increased risk for brain cancer was concentrated among subjects with the shortest time since first employment and no clear pattern by duration of employment was observed.

An increased risk for pleural cancer was observed in the whole cohort, suggesting a possible past asbestos exposure. Most cases occurred in subjects with duration of employment and latency longer than 20 years. These data are consistent with some previous epidemiological studies conducted among petrochemical workers in the US (20), Canada (13) and Italy (15), supporting the hypothesis of a significant asbestos exposure in such industrial setting.

As regard skin cancer, we are aware that, because of the low fatality rate of such tumors, mortality studies are not the best tool to detect a small (if existing) increased risk. However we find a decreased skin cancer mortality (-45%) based on 3 cases only.

Finally, focusing on lymphoemopoietic cancers, in the whole cohort a modest increased risk was found for myeloid leukemia and an 81% increased mortality was observed for LL. All AML and seven out of 8 cases of LL occurred after 20 years of latency. Both AML and LL showed a near doubled increased risk among workers with the longest duration of employment (≥ 20 years).

Although the small number of the observed events, limits the interpretation of our findings, our results are consistent with the current epidemiological evidence extending to lymphatic leukemia, and particularly CLL, the spectrum of hematological malignancies associated with occupational exposure to benzene (10, 11, 14, 16, 17, 21).

The meta-analysis of occupational cohorts by Vlaanderen et al supported the evidence of an association between benzene exposure and MM, ALL, and CLL (21, 22). We did not observe increased risk for MM but we did for lymphatic leukemia, although not statistically significant. Notably the most prominent increase in LL was among workers with the longest duration of employment (≥ 20 years), the same subgroup with a doubled risk of AML (see table 4). For this purpose it is important to underline that, as stated by Vlaanderen and collaborators, the power of detecting AML increased risk (a well-established benzene exposure related effect) is a valuable indicator of good methodological quality for studies investigating benzene health effects (21).

We did not find increased risk for CML concordantly with most recent meta-estimates (10, 19, 20, 22).

The high proportion of successful vital status ascertainment of cohort members, the very low number of missing causes of death, and the almost 50 years of follow-up (49 years) are the major strengths of our study. Being more prolonged than most published epidemiological studies, our mortality follow-up study allowed to properly investigate risk of long latency diseases.

The main limitation is the lack of information on the job and the exposures of the individual cohort members. Only date of hiring and ceasing employment were available; we calculated duration of employment as a proxy for exposure. In addition, we could not formally investigate the role of benzene exposure due to the lack of quantitative data. Scanty environmental measurements were available only in two plants, Milano and Cagliari, for a limited time period and very few departments. In the Milano plant, environmental data (58 samples) were collected in 1984 and 1985 in the Production and Moving departments, where 28% and 41% of the samples respectively, showed benzene air levels above 1 ppm (the recommended European occupational exposure limit).

In the Cagliari plant, 118 samples were collected in more recent years (1988, 1993, 1996 and 1998). Most measurements in 1988 were below 1 ppm, and measurements collected in the '90 revealed benzene

levels always below 1 ppm (and below 0.5 ppm in 98% of samples in 1998).

These data do not allow to estimate benzene exposure over the long study period, but they document the decline in benzene exposure over recent decades: benzene levels were most likely higher in the past, when cohort members began their employment at the oil refineries.

Death certificates are not the most accurate diagnostic tool for lympho-hematopoietic neoplasms; due to the long survival of patients affected by several subtypes, and particularly CLL and HL, risk can be substantially underestimated when using mortality data in respect to incidence data (14, 19).

There are several potential time-related confounders in occupational cohort studies, summarized as the healthy worker effect (HWE) (4). In our study population lower mortality rates for circulatory, and pulmonary diseases suggest that HWE actually occurred. Moreover, HWE increases with duration of employment because of a self-selection of workers with longest employment duration, also called "healthy survivor effect". We observed the highest risk of leukemia in the subgroup with the longest duration of employment, an excess that might have been even more pronounced in the absence of HWE.

No information about smoking habits were available for our workers. Smoking is a well-established risk factor for several cancer sites including hematopoietic neoplasms (9). However, lung cancer risk (the most frequent tobacco-related cancer), as well as non-neoplastic respiratory and circulatory disease mortality, had decreased in our cohort, suggesting smoking as an implausible confounder in our study. The decreased mortality from lung cancer in our cohort might have been a beneficial outcome of the no smoking policy introduced in these plants for safety purposes, which might have contributed to diminish smoking among cohort members in respect to the general population.

In conclusion, our results are consistent with the previously reported excess mortality from pleural and hematopoietic malignancies among oil refinery workers. In particular, they provide support to the hypothesis of an increased risk of hematopoietic diseases other than AML (8).

But larger studies supported by an accurate exposure assessment are warranted to properly identify a causative role of benzene, especially at the current very low exposure levels.

NO POTENTIAL CONFLICT OF INTEREST RELEVANT TO THIS ARTICLE WAS REPORTED BY THE AUTHORS

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